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THE USE AND THE VALUE OF TUBERCULIN IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS.

LOUIS HAMMAN.

BALTIMORE.

In the last ten years the literature on the diagnostic use of tuberculin has been enriched by a large number of important and exhaustive contributions,[1] and we are now in a position to pass at least a temporary judgment on the value and the shortcomings of the method. After the first few years of extensive application of tuberculin following its introduction in 1890[2] its use in diagnosis was largely abandoned when in treatment it had proved not only valueless but harmful.[3] The tuberculin revival, in the midst of which we are at present, is an outcome of the modern sanitarium movement, the ever-increasing demand for earlier and earlier diagnosis being the motive and abundant material and convenience for careful observation the opportunity. Bridging the two periods is the work of a few such enthusiasts as Trudeau, Fraenkel, Spengler, Petruschky, Möller and others who kept interest alive and communicated it to their near associates. Dr. Trudeau's influence has always been strongly felt in Johns Hopkins Hospital, and tuberculin, while not extensively, still has been continuously employed for diagnosis during the past fifteen years.

For fourteen months we have used tuberculin rather largely in the Phipps Dispensary both in diagnosis and treatment, having made in round numbers about five thousand injections. Naturally we see a great many cases in which, after a careful application of the usual methods of diagnosis, doubt remains. In an effort to reach greater assurance we have turned to tuberculin, and I have analyzed the first 94 cases injected as a text for this paper. We have nothing new to repeat nor any startling modifications to suggest, but we have made a number of observations of great interest to us which may serve as illustrations to point a more reasonable attitude toward tuberculin. Prevalent misstatements about the best methods of use and the value of tuberculin in diagnosis might

1. Beck: Deutsch. med. Wchnschr., 1899, Nos. 5-9. Möller and Kayserling: Ztschr. f. Tuberk., 1902, iii, 279. Hammer: Beitr. z. Klin. d. Tuberk., 1903, i, 325. Löwenstein and Rappaport: Ztschr. f. Tuberk., 1904, v, 485. Bandelier: Beitr. z. Klin. d. Tuberk., 1904, ii, 285. Köhler: Tuberculin u. Organismus, Fischer, Jena, 1905. Roth-Schulz: Beitr. z. Klin. d. Tuberk., 1906, vi, 167. Roepke: Ztschr. f. Tuberk., 1907, x, 412. And many others.

2. Koch: Deutsch. med. Wchnschr.

3. Most important early literature on tuberculin may be found in Klinisches Jahrbuch, Ergänzungsband, 1891.

be offered as a justification. One of our most prominent American pediatrists has recently written about tuberculin and says that the dose for an infant or young child is from two to five milligrams. Such an unqualified statement, I believe, might be productive of much harmful misunderstanding; and that four milligrams may be followed by serious results a case he cites illustrates. One reads so frequently that all of the patients in a certain group either had tubercle bacilli in their sputum or reacted to tuberculin. The impression is conveyed that these two pieces of evidence are of equal value, which they by no means are; and one gets the further impression that a reaction to tuberculin absolutely settles a doubtful diagnosis, which it certainly does not. A German author,[4] speaking of suspicious cases, writes that "Koch's old tuberculin

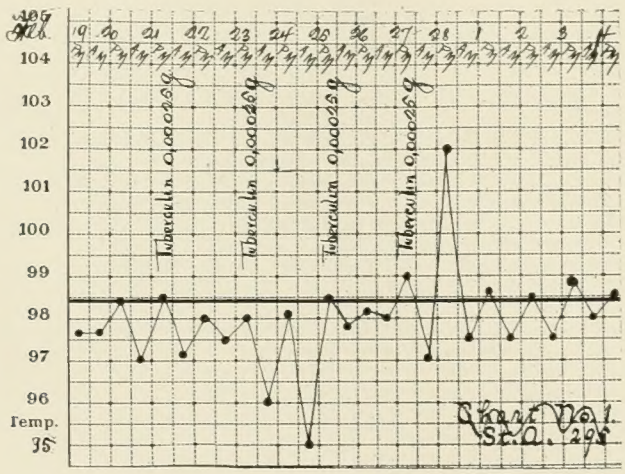

Chart No. 1.

is the sovereign means with which to establish the proper diagnosis with absolute certainty." Bandelier,[5] too, says that "the quintessence of tuberculin diagnosis is in the 'sicherstellung'—the making absolutely sure—of the diagnosis in doubtful cases." This term "sicherstellung" is frequently met in the German literature, and it is a matter of first importance to make quite clear how far its use is justified.

THEORETICAL CONSIDERATIONS.

There is no more interesting phenomenon in the whole range of medicine than the tuberculin reaction, and we are still far from a satis-

4. Ziegler: München. med. Wchnschr., 1907, p. 1320.
5. Beitr. z. Klin. d. Tuberk., 1904, ii, 285.

factory understanding of even its fundamental principles. Here is a substance, practically inert toward healthy animals, which under certain conditions becomes highly toxic toward subjects affected with even a trivial tuberculous lesion. A single focus of disease may so change every cell in the body that when a small amount of tuberculin is brought in contact with it a violent reaction ensues. A drop placed on a mucous membrane or rubbed into the skin or injected into the subcutaneous tissue produces extensive local changes. We know little about the nature of these changes. Since Wasserman and Bruck[6] have demonstrated the presence of antituberculin in the tissues and at times even in the blood we have come to view such changes as the expression of a specific reaction between the two substances, with perhaps a stimulation to the further production of antibodies. We are not yet sure that tuberculin itself causes this remarkable change in the body cells, for, desirable as such

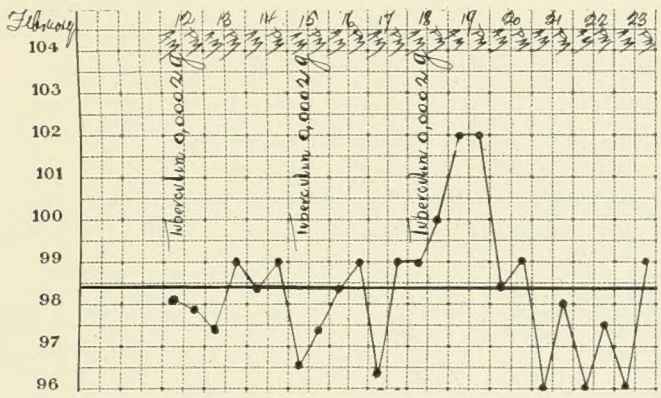

Chart No. 2.

information may be, it still remains to be proved that a normal animal can be rendered hypersensitive by the repeated injection of tuberculin. The fever and the constitutional symptoms are almost certainly due to a substance other than tuberculin, which is newly formed or produced in excess under the stimulation of the latter substance. The summation theory is no longer worthy of consideration. Wasserman believes that he has demonstrated the constant presence of antituberculin in tuberculous foci, and conceives that the tuberculin reaction consists in a local union of tuberculin and antituberculin, with the anchoring of comple-

6. Wasserman and Bruck: Deutsch. med. Wchnschr., 1906, No. 12. Wasserman and Bruck: Münch. med. Wchnschr., 1906, No. 49. Wasserman and Citron: Ztschr. f. Hyg., 1906, lii, 238.

ment, this new substance acting as a ferment on the tuberculous tissue and the absorption of the products of digestion causing fever and the characteristic constitutional symptoms. This is merely a new garb for the hypothesis which Ehrlich[7] advanced in 1900.

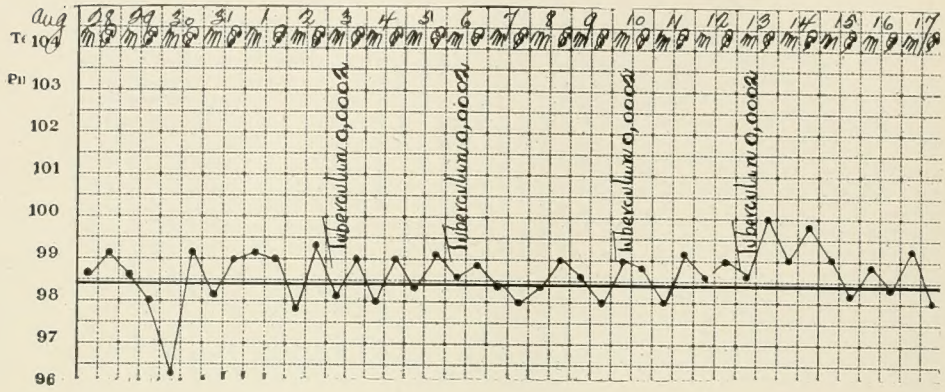

Chart No. 3.

In both of these hypotheses the presence of a tuberculous focus is an essential. Wasserman's views practically resolve themselves into a question of toxin and antitoxin, the absence of a reaction in a tuberculous patient being interpreted as a blocking off of the toxin from the tubercu-

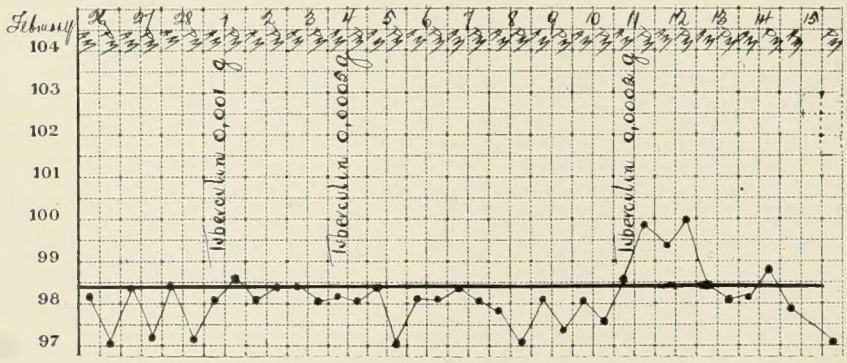

Chart No. 4.

lous tissue by neutralization in the blood stream. In some patients, particularly in those long treated with tuberculin, he has been able to demonstrate the presence of complement deviating substances in the blood, but

7. Internat. Kong. f. Hyg., 1900.

in only a very small proportion of cases. The work of Morgenroth,[8] however, and particularly the detailed considerations of Wolff-Eisner,[9] indicate that the conditions are not as simple as such a conception would

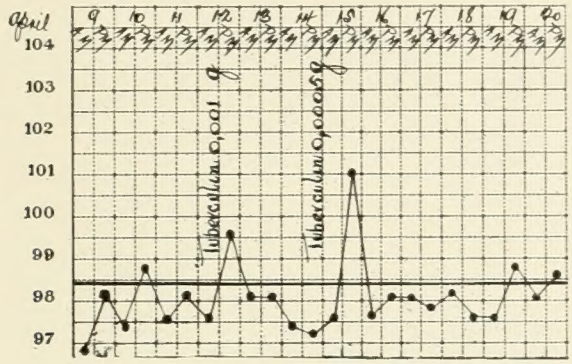

Chart No. 5.

lead us to believe. In the first place there is no evidence to show that the union of toxin and antitoxin ever gives a local reaction; then, too, all recent work on tuberculin demonstrates that its active agent is the al-

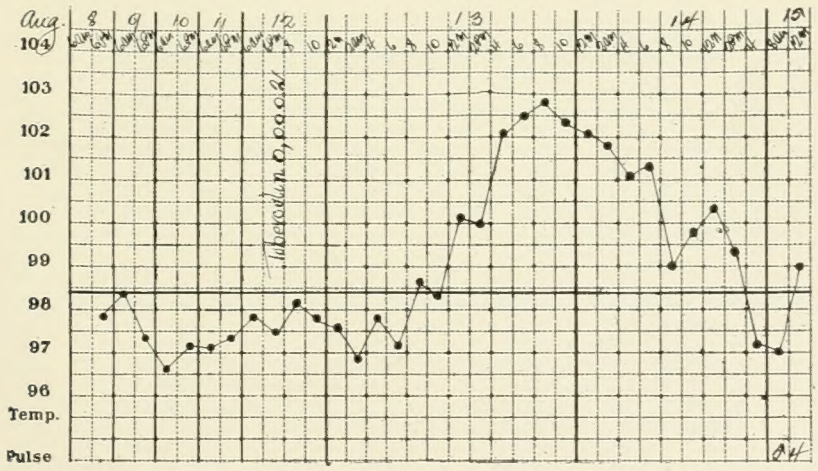

Chart No. 6.

buminous portion of the bacilli themselves which produces no antitoxin; further, a number of observations tend to show that reactions to tubercu-

8. Morgenroth and Rabinowitch: Deutsch. med. Wchnschr., 1907, No. 18.
9. Beitr. z. Klin. Tuberk., 1908, iv, No. 1.

lin may occur in the absence of tuberculous lesions, and, lastly, Wasserman's view fails to take into account the important principle of hypersusceptibility—perhaps better known under the terms allergie and anaphylaxis.

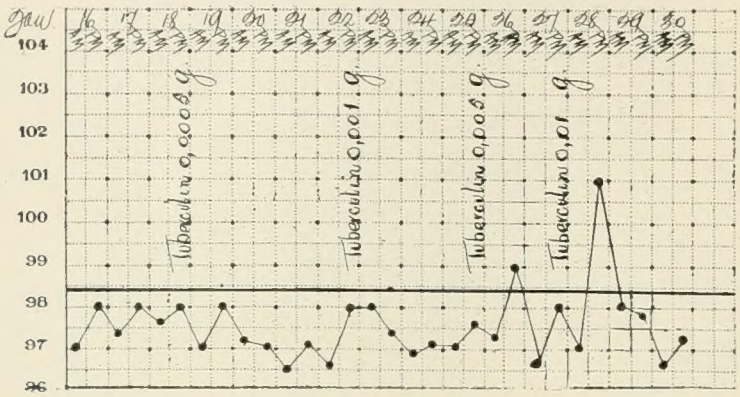

Chart No. 7.

Tuberculin differs according to the manner of its preparation. It is well known that many of the older preparations contained tubercle bacilli

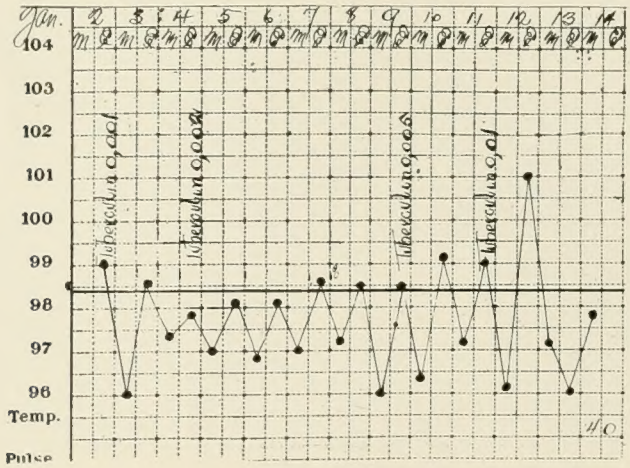

Chart No. 8.

in large number,[10] but if put through a Berkefeld filter no such gross particles are present. Nevertheless these two specimens will act in an

10. Wolff-Eisner: Beitr. z. Klin. d. Tuberk., 1908, ix, No. 1.

identical manner, displaying differences in degree, but never in the quality of reactions. Löwenstein[11] was first to draw attention to the development of hypersusceptibility to tuberculin in tuberculous patients. His instances and tables are conclusive, and the phenomenon has become the common observation of every one using tuberculin. This principle of hypersusceptibility is the fundamental symptom of the serum disease[12] and its production a property of all albuminous bodies. Preisich and Heim[13] were the first to demonstrate that animals who had no tuberculous lesion would react to tuberculin. In two instances they were successful in introducing into the peritoneal cavity of guinea-pigs capsules containing tubercle bacilli, and the animals soon acquired tuberculin hypersensitiveness, showing at autopsy no tuberculous lesions. Walle[14] and Maussu[15] report similar observations.

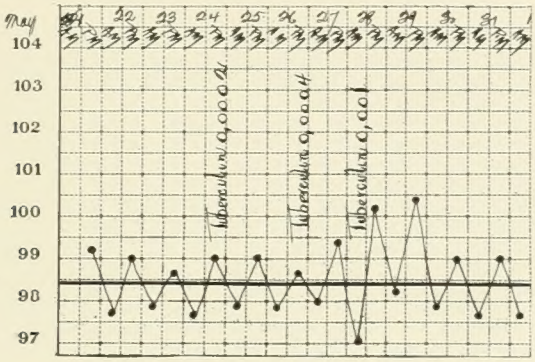

Chart No. 9.

The views of Wolff-Eisner seem to fit best into what we at present know of the tuberculin reaction and, shorn of their technicality, are briefly this: Tuberculin, which really consists of ultramicroscopic portions of the tubercle bacillus, produces the same effects in the animal body as tubercle bacilli, except that the latter are capable of multiplication. The local tuberculin reaction is caused by an accumulation of lymphoid cells, and true giant cells are formed. The injection of living tubercle bacilli is followed by the development of hypersensitiveness the same as that which follows tuberculin injections. As in typhoid and

11. Löwenstein and Rappaport: Ztschr. f. Tuberk., 1904, v, 285. Anderson: Hygienic Laboratory Bulletin, No. 26, 1907.
12. von Pirquet and Schick: Die Serumkrankheit, Vienna, 1905. Rosenau and
13. Centralbl. f. Bakteriol., 1902, p. 712.
14. Compt.-rend. Soc. de biol., lxi, No. 28.
15. Semaine méd., 1907, No. 49.

cholera, the immunity reaction in tuberculosis depends on the presence of lysins. The tuberculin reaction is not due to the tuberculin itself nor to the disintegration at the site of disease, but to a new toxic substance formed by the action of the lysins on the albuminous portion of the bacillary body. For this toxic substance to become active the organism must be in a condition of hypersensitiveness. There are, then, two factors to be considered: the presence of lysins and the condition of hypersusceptibility. The lysins may be artificially increased and are the bodies which deviate complement in Wasserman's experiment. The hypersensitiveness varies under conditions of which we are still ignorant, but it, too, may to some extent be stimulated or obtused. Normally there is no lysin present, or so small an amount that when tuberculin is injected the transformation goes on so slowly that the newly formed toxin causes no appreciable effect. Under continuous minimal stimula-

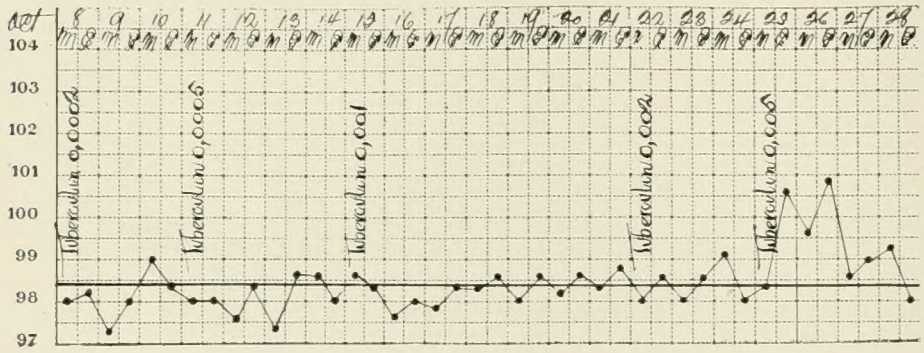

Chart No. 10.

tion the quantity of lysin increases, and the transformation then occurs so rapidly that after an injection intense toxic symptoms occur. The toxin causes a local reaction at the site of injection, constitutional symptoms and an inflammatory reaction at the site of the tuberculous lesion. During the inoculation of small doses of tuberculin hypersensitiveness is developed. Variation in susceptibility to tuberculin in tuberculous subjects depends essentially on variation in hypersensitiveness, lysins probably being present in all.

These theoretical considerations are of great importance for a proper appreciation of the clinical significance of the tuberculin reaction. They are the basis of a reasonable understanding of the question why many healthy individuals react and why some tuberculous subjects do not and give the foundation to our present method of conducting the reaction. Any number of instances of developing hypersensitiveness might be pre-

sented. Charts Nos. 1, 2 and 3 are examples. In all of them the repetition of a small dose has finally liberated a reaction. We can no longer even consider the explanation that Bondelier urges that these reactions are the expression of a summation. Löwenstein disposes of such a view in his original communication. The hypersensitiveness following tuberculin administration may last for a year. Not only can we get a reaction by repeating the same small dose, but occasionally the hypersensitiveness develops in a most striking manner with decreasing doses. Such a reaction is uncommon, but we have two illustrations. In Chart 4 the reaction is seen to follow 1/5 mg. after 1 mg. and ½ mg. were negative. In Chart 5 there is seen a marked reaction to ½ mg. after a slight reaction to 1 mg.

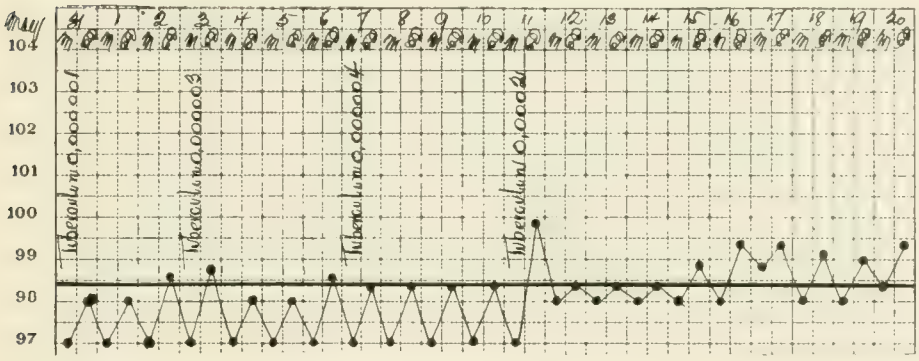

Chart No. 11.

THE SIGNIFICANCE OF TUBERCULIN HYPERSENSITIVENESS.

We know that many healthy individuals are unaffected by as much as 50 mg. of tuberculin. What is the significance of this marked sensitiveness to the reagent? There are two standpoints from which we may consider the specificity of tuberculin: First, will only those individuals who are affected with tuberculosis react, and, second, will tuberculous individuals react only to tuberculin, or will other substances produce the same effect? Our theoretical considerations, if they are valid, would certainly answer the first question in the affirmative, and we have a large statistical material from which to judge of practical results. In all such tests autopsy can alone be the deciding evidence. Naturally in man such control is impossible, but the extensive application of tuberculin to veterinary practice has given us the desired opportunity. Fraenkel[16] has

16. Ztschr. f. Tuberk., i, No. 4.

collected 8,000 observations on cattle, and the results of the tuberculin reaction have coincided with the autopsy findings in all but a little over 2 per cent. Voges,[17] in 7,327 observations, found a percentage error of 2.7. Nocard,[18] in 124 instances, found only one that did not coincide. Bang[19] has reviewed the question extensively and points out two sources of error. A certain number of cattle react in whom at autopsy no tuberculous lesion is found. Such an occurrence is uncommon and decreases in frequency in inverse proportion with the care exercised in searching for the lesion. It is no matter for wonder that a few tubercles no larger than the head of a pin will occasionally be overlooked. These animal observations impress on us particularly how very slight, indeed, a tuberculous lesion may be that has produced hypersensitiveness. A more important source of disagreement between test and autopsy is the not infrequent failure of a manifestly tuberculous animal to react. Such an oc-

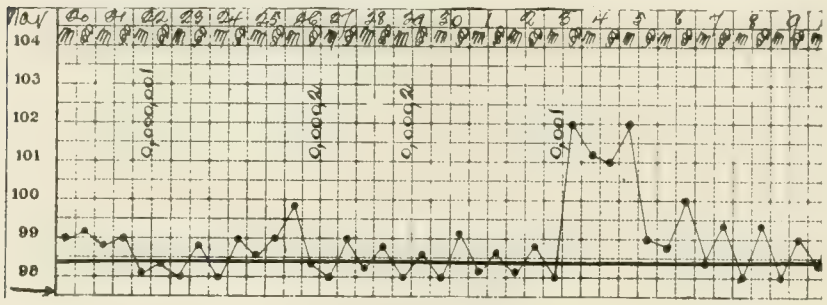

Chart No. 12.

currence is well appreciated in the study of human tuberculosis and would not enter as a disturbing factor in the clinical use of tuberculin.

It may seem trivial now to stop to consider the second viewpoint of tuberculin specificity, but it has played an important rôle in the history of its use. Rosenbach suggested when tuberculin was first introduced that the reaction depended on the instability of the heat-regulating mechanism of tuberculous patients and could be produced as well by numerous other bacterial poisons. Tuberculin, he contended, would cause fever in convalescents and patients in a "weakened condition" as readily as in the tuberculous. Matthes,[20] in 1894, investigated the effects

17. Ztschr. f. Krankenpfl., 1904, xxvi, Nos. 5 8.
18. Nocard, cit. Köhler: Tuberculin u. Organisms, Fischer, Jena, 1905.
19. Tuberculosis, Leipsic, iii, No. 5.
20. Deutsch. Arch. f. klin. Med., 1894.

of albumoses on tuberculous patients and, finding their injection produced reactions, suggested using solutions of these instead of tuberculin for the test. His work is still of great interest, indicating that the tuberculin reaction is chemically perhaps a group reaction, all albumoses being effective, but the specific albumose of the tubercle bacillus in far smaller doses than any other. The serum of Hayem, a 0.7 per cent. salt solution, at one time threatened to destroy belief in the specificity of tuberculin. Hutinel,[21] in an elaborate series of experiments, concluded that results with its use were as satisfactory as with tuberculin and that it was to be preferred on account of its harmlessness. Combemale and Mauton,[22] however, after extensive observation, showed the fallacy of Hutinel's conclusions. We can very safely say that tuberculin hypersensitiveness depends on the presence in the body of certain specific

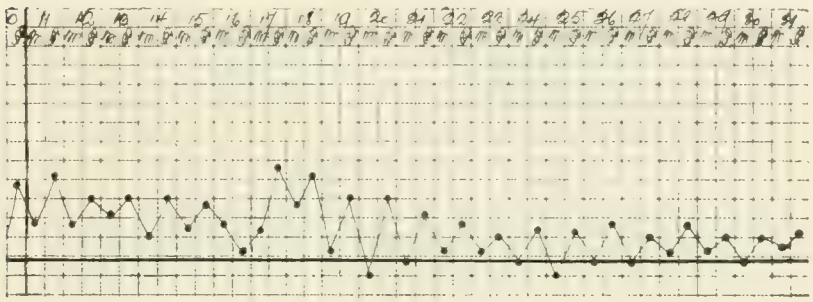

Chart No. 12—Continued.

substances which can arise only through intimate association with the tubercle bacillus and that the reaction is more than an expression of thermal instability.

THE CLINICAL FEATURES OF THE TUBERCULIN REACTION.

We may refer very briefly to our methods of observation, as they are those in general use. Fifteen of our cases received their injections at Eudowood Sanitarium, 43 at St. Agnes Hospital and 36 were treated as ambulant cases in the Dispensary.[23] In institutions the method of control is very simple. After at least one, and usually more careful exami-

21. Semaine méd., 1895, p. 117.

22. Cong. de méd. interne, Lille, 1899.

23. I am indebted for help in the observation of our patients particularly to Drs. S. Wolman, assistant in the Phipps Dispensary; A. M. Forster, resident physician Eudowood Sanitarium, and H. H. Hazen, resident physician, St. Agnes Hospital.

nation the patient's temperature is recorded, and if not above 99 for two days injections are begun. During the test period the temperature is taken every two hours. After each injection the patient's symptoms are recorded and the chest examined. As a rule, injections are given every second day, but at times a longer interval is allowed to elapse. Where time was pressing we have given some injections even when the temperature had previously been a little over 99, but this practice clouds the results and should be condemned. The ambulant patients were taught to record their own temperature and pulse rate and to keep a daily record of their symptoms. If after an injection their temperature goes to 99.4 or over, they report at the dispensary the following morning for examination, or if they are too ill they are visited at their homes. Injections are given twice a week. The method has proved very satisfactory, indeed, and we are making more and more of our observations in the dispensary instead of transfering the patients to a hospital.

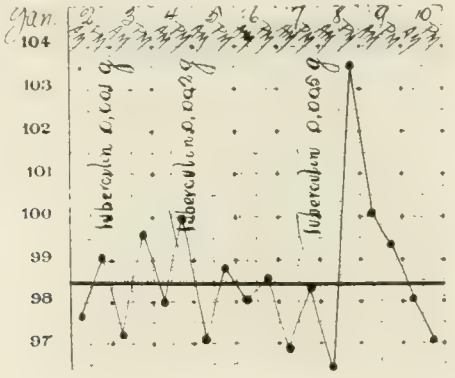

Chart No. 13.

In every tuberculin reaction there are four essential features which are the object of careful clinical observation: the temperature, the constitutional symptoms, the local reaction and the focal reaction.

When a patient reacts to tuberculin the temperature, as a rule, begins to rise in 6 to 12 hours, reaches its height in 12 to 24, and is normal again in 24 to 36. Unfortunately in analyzing our histories the length of time between the injection and the beginning of the rise was noted in only nineteen as follows:

In 10 instances, less than six hours.
In 6 instances, between six and twelve hours.
In 3 instances, between twelve and twenty-four hours.

It is uncommon for the reaction to be delayed over 24 hours, but Dr. Wolman has given me the notes of a case in which the temperature did

not begin to rise until 36 hours after the injection. In 64 observations the time between the injection and the height of the reaction was as follows:

In 2 cases, less than six hours.
In 14 cases, between six and twelve hours.
In 38 cases, between twelve and twenty-four hours.
In ten cases, over twenty-four hours.

The longest time was 36 hours and the shortest four. The duration of the reaction was as follows:

In 9 cases, less than twelve hours.
In 19 cases, between twelve and twenty-four hours.
In 25 cases, between twenty-four and forty-eight hours.
In 11 cases, over forty-eight hours.

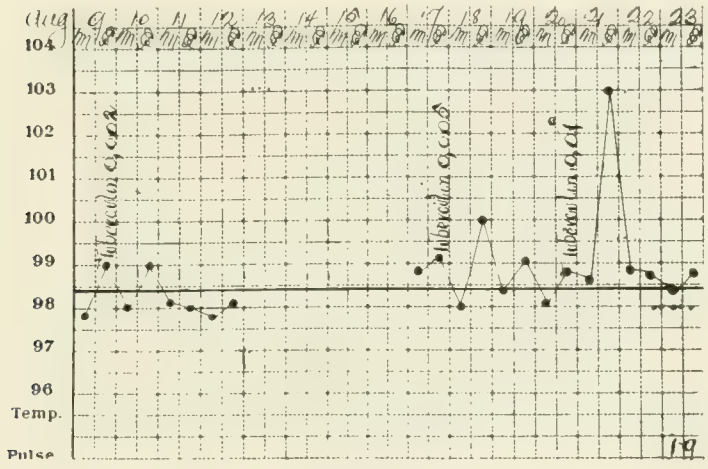

Chart No. 14.

The longest durations were ten days, over one week and three weeks.

It is of interest to know if the duration and severity of a reaction bear any relation to the size of the dose which liberates it. Such figures would be of value, if the reactions always occurred at the first injection, if we had any method of estimating how large such a dose should be. As it is, we must grope about in the dark until we find the proper dose, and in our experimentation the susceptibility of a patient may be greatly altered. To give 1 mg. after having given a few fifths is quite different from starting with 1 mg.

In 9 cases with a duration less than 12 hours, the liberating dose was under 1 mg. in 3 cases and 1 mg. or over in 6 cases.

In the 19 cases with a duration between 12 and 24 hours, the liberating dose was under 1 mg. in 5 cases and 1 mg. or over in 14 cases.

In the 25 cases with a duration between 24 and 48 hours the liberating dose was under 1 mg. in 5 cases and 1 mg. or over in 20 cases.

In the 11 cases with a duration of 48 hours or over, the liberating dose was under 1 mg. in 3 cases and 1 mg. or over in 8 cases.

By transposing these results we have the following: Of 16 cases reacting to doses under 1 mg., in 8 the duration of the reaction was less than 24 hours; in 8 the duration was over 24 hours. Of 48 cases reacting to doses of 1 mg. or over, in 20 the duration of the reaction was less than 24 hours; in 28 the duration was over 24 hours.

Certainly there is no striking difference in the duration of the reaction after large or small doses. According to the height which the temperature reaches, we may divide our cases into three groups: mild reac-

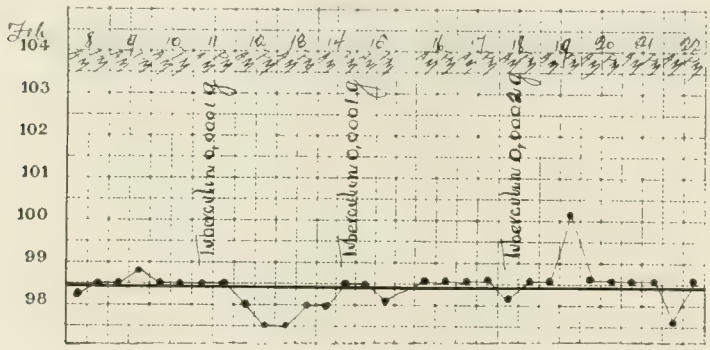

Chart No. 15.

tions in which the temperature remains under 100; moderate reactions, between 100 and 102; severe reactions, over 102.

Of 23 cases reacting to doses under 1 mg., 6 gave a severe reaction, 12 gave a moderate reaction, and 5 gave a mild reaction.

Of 53 cases reacting to doses of 1 mg. or over, 20 gave a severe reaction, 29 gave a moderate reaction, and 4 gave a mild reaction.

There is a higher percentage of severe reactions to the larger than to the smaller dose. Hammer, from an analysis of 180 cases, concludes that duration and severity of a reaction bear no relation to the size of the dose. In his series, however, he begins with 1 mg.

As our figures show, the usual type of temperature curve in a tuberculin reaction is a gradual rise to the high point and gradual fall to the normal as seen in the characteristic Chart 6.

Occasionally the temperature rises abruptly, at times the onset being marked by a chill so that only a few hours may elapse between the beginning of the rise and the fastigium as in Chart 7. The fall may be as abrupt as the rise, the whole reaction being over in four to six hours,

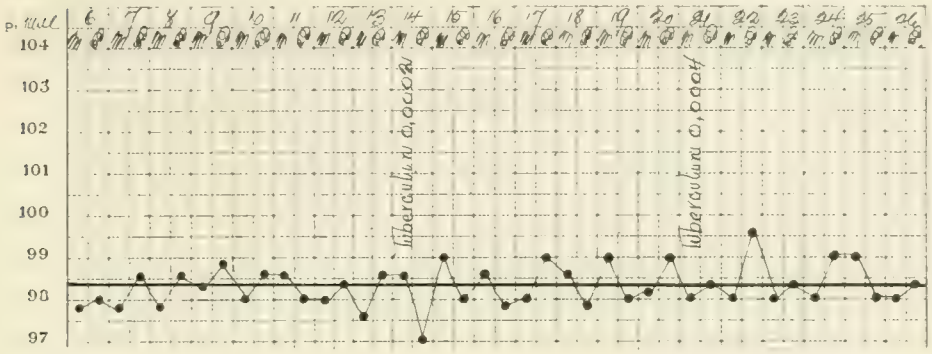

Chart No. 16.

as in Chart 8. Not infrequently the first elevation is followed by a secondary rise, as in Chart 9. Chart 10 is a good example of a sustained reaction. Of special importance are the cases in which the reaction is followed by a continued elevation of temperature for days or even weeks, as in Charts 11 and 12.

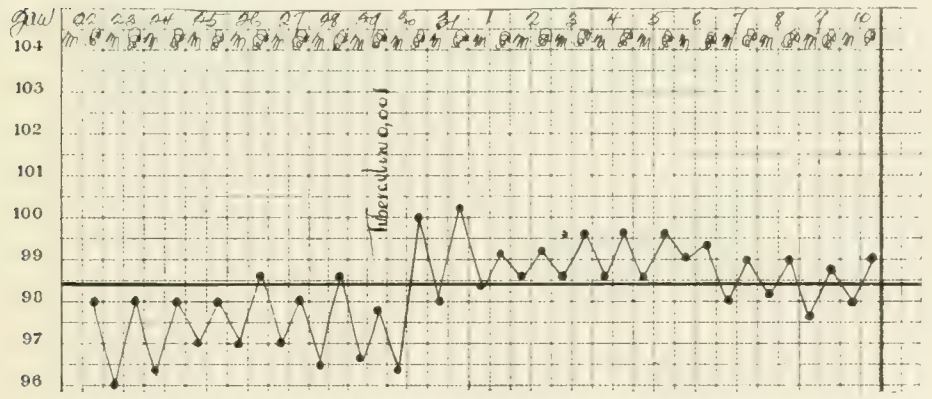

Chart No. 17.

The constitutional symptoms are as varied in character and in intensity as the temperature curve. They begin with the onset of the fever, reach the maximum at its highest point and gradually subside. When the temperature reaches normal the patient feels well again, except after

unusually severe reactions, when prostration and malaise may persist for days. The severity of the symptoms and the height of the fever bear no constant relation, however; indeed, the two seem often to be quite independent of one another. In many cases, as those shown in Charts 13 and 14, the constitutional symptoms are very slight, though the temperature reaction is over 102, while in others, as in cases shown in Charts 15 and 16, the constitutional symptoms are intense, though the temperature does not go over 100.

In the 17 cases with no marked constitutional symptoms:

3 had a slight febrile reaction.
10 had a moderate febrile reaction.
4 had a severe febrile reaction.

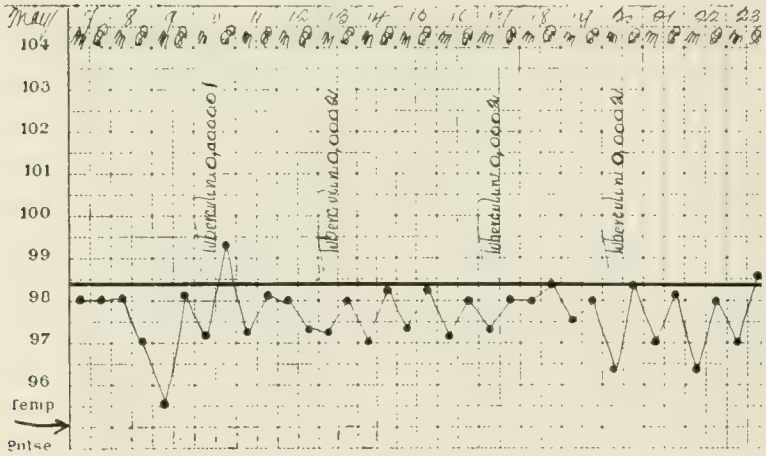

Chart No. 18.

In 43 cases with well-marked constitutional symptoms:

3 had a slight febrile reaction.
25 had a moderate febrile reaction.
15 had a severe febrile reaction.

In 14 cases with intense constitutional symptoms:

3 had a slight febrile reaction.
5 had a moderate febrile reaction.
6 had a severe febrile reaction.

I have made no attempt to analyze the various symptoms which arise and their frequency. This has been done in a thorough manner by Hammer. In typical cases patients invariably compare their symptoms to those of grippe. There is marked prostration, headache, intense pain in all the joints and limbs, and frequently nausea and vomiting. These symptoms may at times become alarming. No. 17 is the chart of a

patient, with a suggestive history and indefinite physical signs, who received an initial dose of 1 mg. Although the temperature rose only to 100.2, she became extremely ill. Almost incessant vomiting for three days with severe abdominal pain so prostrated her that the attendants and even the resident physician were seriously concerned about her safety. She recovered completely, however, and to all appearances suffered no permanent ill effects. Two of our cases became delirious; one, an epileptic, had a convulsion at the height of the reaction; two cases had an extensive eruption of herpes, and one unilateral sweating on the side of the injection. It is remarkable how frequently constitutional symptoms are present without a rise in temperature. For instance, the patient whose case is represented in Chart 18 received four injections of 1/5 mg.,

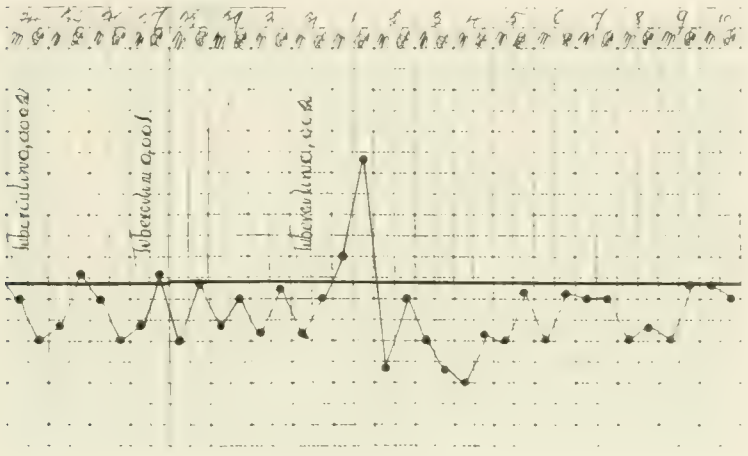

Chart No. 18—Continued.

then 1 mg. and then 2 mg. After the first dose she complained of general malaise and prostration, and after 1 mg. was quite ill. There is, however, no elevation of temperature until 2 mg. are given. It is common to have patients say, "Each one of these injections makes me very sick, but I have no fever."

The local reaction at the site of injection consists in redness, swelling and pain. The regional glands, too, are often swollen and tender. Unfortunately, its presence or absence has not been regularly noted in our records, but I can recall no single instance in which a patient reacted and it was absent. It may not be present after the particular dose which liberates a reaction, but when it is absent then it has been well marked after previous injections. Even more frequently than the constitutional

symptoms it is a forerunner of the coming reaction. It is almost the rule for patients to complain of pain and swelling after the doses preceding the one that gives a reaction. At times the local phenomena with the accompanying glandular swelling are the most prominent features in the reaction. Even with slight fever and almost negligible constitutional symptoms, a tumor as large as one's fist may arise at the point of injection. Curiously, too, a patient may show such a local reaction and never give either a rise of temperature or complain of constitutional symptoms even after much larger doses. We have two such instances. The patient whose case is shown in Chart 19 received four doses of 1/5 mg., one each of ½ mg., 2 mg. and 10 mg. After the first dose the temperature rose to 99.4 and there was marked pain and swelling at the site of the injection. After the second dose there was no rise of tem-

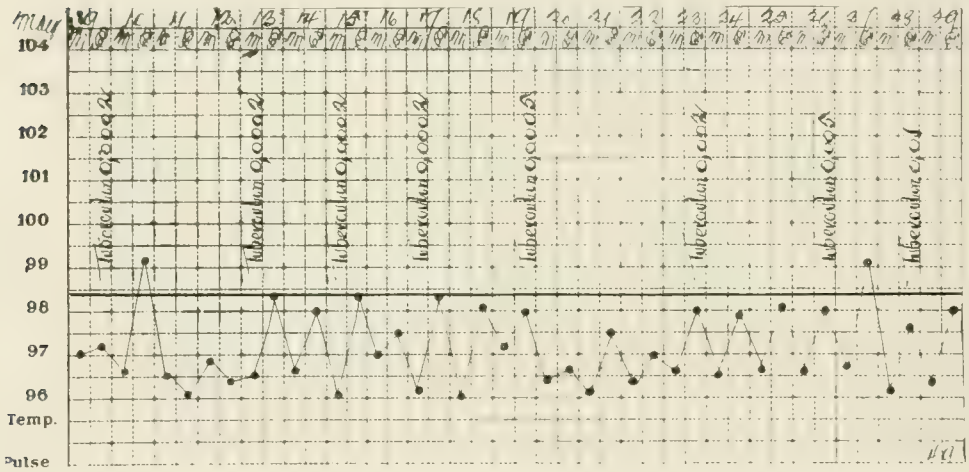

Chart No. 19.

perature and the local reaction was slight. From then on there was neither local nor febrile reaction, except that after 5 mg. the temperature went to 99.2. The patient never complained of constitutional symptoms. In the case shown in Chart 20 there was a marked local reaction after the first two injections.

When a tuberculous lesion is situated externally very remarkable changes are seen to occur during a tuberculin reaction. The focus becomes swollen and red and moist, and if the inflammatory reaction is severe it is followed by necrosis and sloughing. If the lesion is in the lung, evidence of such a reaction may be obtained from the symptoms and from physical examination. The characteristic symptoms are pain

in the chest and increased cough and expectoration. Occasionally there is hemoptysis, and tubercle bacilli, absent before, may appear in the sputum for the first time. In the case shown in Chart 21, with indefinite pulmonary signs, four sputum examinations were negative before the reaction; the fifth, immediately after, positive. In the case shown in Chart 22 several examinations before the reaction were negative; the one immediately after, positive. Möller reports similar observations in 4 of 123 cases. Our 2 instances occurred among 63 suspected cases that reacted. Fraenkel,[24] in 167 cases, found none that showed tubercle bacilli in the sputum after the reaction where they had been absent before. Hammer observed it once in 164 reactions.

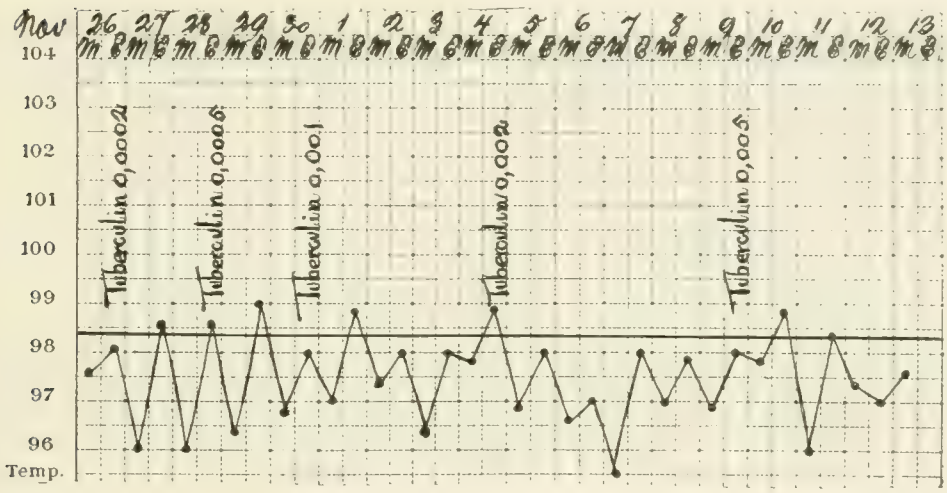

Chart No. 20.

Symptoms of a focal reaction in the lungs are not uncommon. In 60 doubtful cases that reacted, they were noted in 18 and marked as definitely absent in 17. In the remaining 25 cases no note is made about the condition, which means in practically all of the cases that the symptoms were not present. Of the 18 cases, 10 complained of increased cough, and 4 of these of increased sputum; 9 complained of pain in the chest. Of 13 cases with definite signs of a pulmonary lesion, 8 gave definite focal symptoms, and in only one the note is made that they were absent.

The physical signs of a focal reaction in the lung consist of changes in the character of the breath sounds and the increase or fresh appear-

24. Fraenkel: Lehr. d. Path. u. Ther. d. Lungenkrankheiten.

ance of râles. The frequency with which such signs are discovered will depend largely on the standard one sets. Roepke found them in 45 per cent. of his cases, but changes in the intensity of the breath sounds or

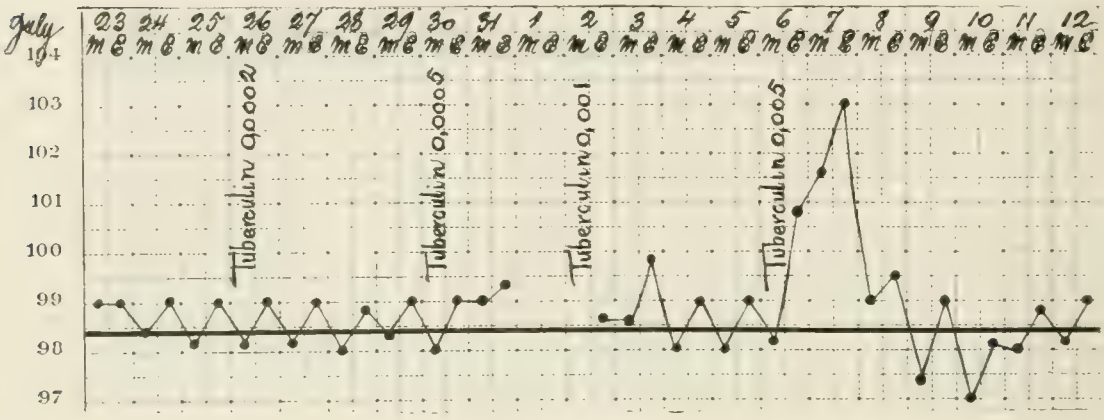
July
23 24 25 26 27 28 29 30 31 1 2 3 4 5 6 7 8 9 10 11 12
m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e
104
103
102
101
100
99
98
97
Tuberculin 0,0002
Tuberculin 0,0005
Tuberculin 0,001
Tuberculin 0,005

Chart No. 21.

increased roughness or an accentuation of inspiratory sacculations he interprets as ample evidence. We have not felt confidence enough in our ability to predicate unmistakably such slight changes and have made the finding of râles where there were none before or a definite increase in

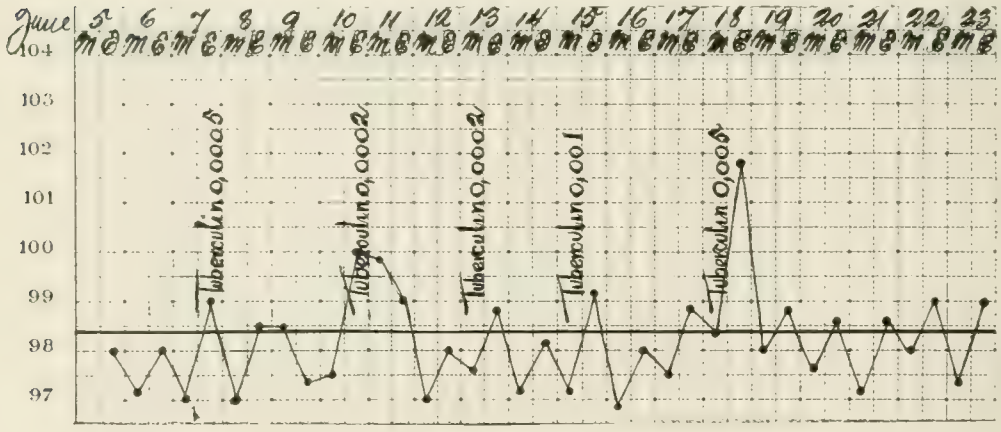
June
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e
104
103
102
101
100
99
98
97
Tuberculin 0,0008
Tuberculin 0,0002
Tuberculin 0,0002
Tuberculin 0,001
Tuberculin 0,005

Chart No. 22.

number or extent of pre-existing râles our criterion. In our 63 suspected cases that reacted there was a well-marked change in the local physical signs in 14; in 9 more there were suggestive but not definite changes; in

37 there was absolutely no change; in 3 the history notes are incomplete. In 13 cases with definite pulmonary lesions, 8 gave signs of a focal reaction, 4 showed no change in the physical signs and in 1 the physical signs almost entirely disappeared. This latter observation is unique in our

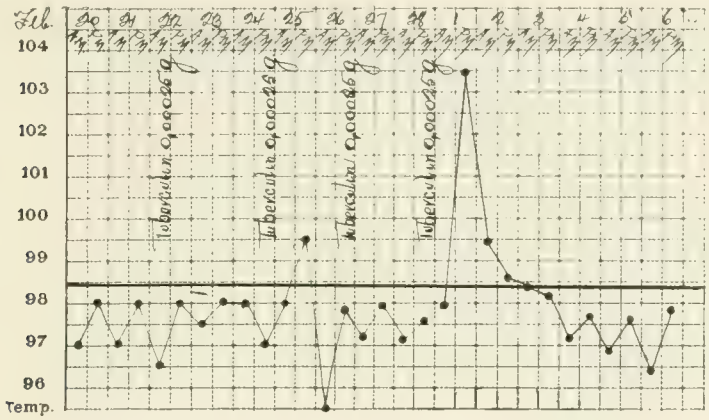

Chart No. 23.

experience. The patient whose case is shown in Chart 23, a girl, aged 17 years, had dulness, suppressed breath sounds and numerous moist and a few sibilant râles over the left back from the angle of the scapula to the base. The lesion having persisted for about six weeks without any change

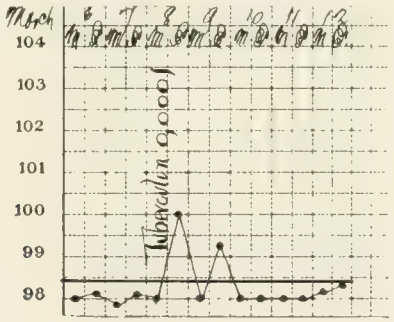

Chart No. 24.

in the physical signs, the patient was given tuberculin. Four doses of ¼ mg. each were administered, and after the second the temperature rose to 99.5, after the fourth to 103.5. There were well-marked constitutional symptoms with cough and expectoration, which had been absent before.

The sputum showed no tubercle bacilli. There was great pain, redness and swelling at the site of injection. After the second dose the râles were fewer in number. After the fourth they had almost completely disappeared. One month later the râles had returned and still persist, almost a year after the reaction. We can not say definitely that the pulmonary lesion in this case is tuberculous; it may have been an unusual coincidence, but a very striking association it is. The absence of the signs of a focal reaction in 46 cases that reacted may be accounted for by supposing that in a certain number the tuberculous lesion was not in the lungs, and in those in which there was a pulmonary focus that the reaction may

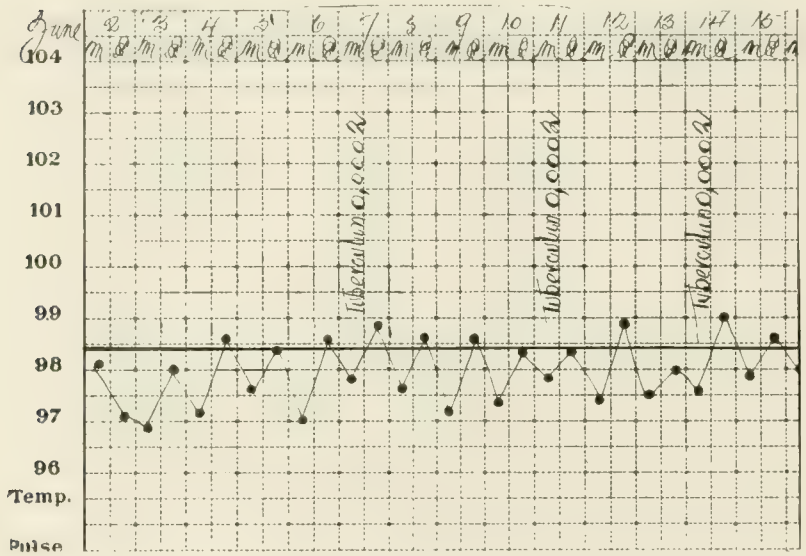

Chart No. 25.

have been too mild to make a difference in the physical signs or the focus too deep to be appreciated by our methods of investigation.

Of 15 suspected cases reacting to doses under 1 mg., 2 gave a focal reaction. Of 45 suspected cases reacting to doses of 1 mg. or over, 12 gave a focal reaction. Of 4 definite cases reacting to doses under 1 mg., 2 gave a focal reaction. Of 8 definite cases reacting to doses of 1 mg. or over, 6 gave a focal reaction. Of the 6 last mentioned, however, 2 showed focal reactions to doses under 1 mg., but no febrile reaction.

Of 6 suspected cases showing a mild reaction, 1 gave signs of a focal reaction. Of 33 suspected cases showing a moderate reaction, 7 gave

signs of a focal reaction. Of 19 suspected cases showing a severe reaction, 6 gave signs of a focal reaction.

These figures show a larger number of focal reactions to high doses and in cases with severe reactions. There is, however, no constant relation between the height and duration of the febrile reaction or the severity of the constitutional symptoms and the focal changes. In Case 42, without a high temperature reaction and with but slight constitutional symptoms, the signs of the focal reaction were particularly striking. In the case shown in Chart 24 they were, too, unusually well marked. In many instances with most severe constitutional symptoms and high fever there was no focal reaction. In the cases shown in Charts 25 and 26,

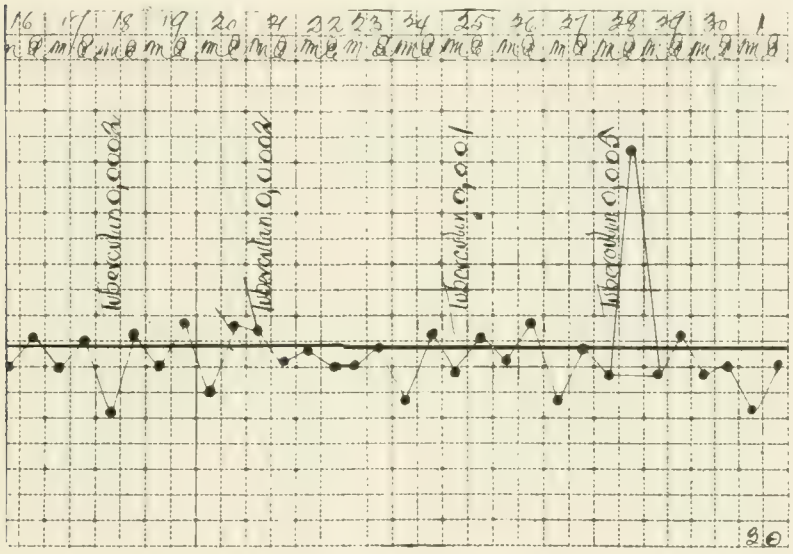

Chart No. 25—Continued.

with definite signs of disease, the focal reaction occurred long before the febrile reaction. In both of these cases the physical signs spread very markedly, and in one case they had not receded after eight months, and in the other they have not completely receded after ten months, although the patient's general condition is greatly improved and all his symptoms have disappeared. The case shown in Chart 27 is of particular interest.

The patient had suggestive symptoms but no definite signs of pulmonary disease. After the second dose of one-fifth of a milligram the temperature rose to 100. After none of the others did it go over 99.2. Following the second injection showers of râles were heard above the

left clavicle and in the left supraspinous fossa. These then disappeared to become evident again after the injection of 10 milligrams. In order to control these observations a second series of injections was given and again after the second and eighth injections the same profuse shower of râles was heard and less numerous râles after some of the intermediate doses. When tuberculin was stopped the râles disappeared.

THE CRITERIA OF A REACTION TO TUBERCULIN.

When the four cardinal symptoms of a tuberculin reaction are present there is no difficulty in making a positive statement; but, as our analysis has shown, such an occurrence is uncommon, and in some instances where only one or even two are present there may be difficulty in definitely deciding that the patient has tuberculin hypersensitiveness. The most important of the four features is without doubt the signs of a focal

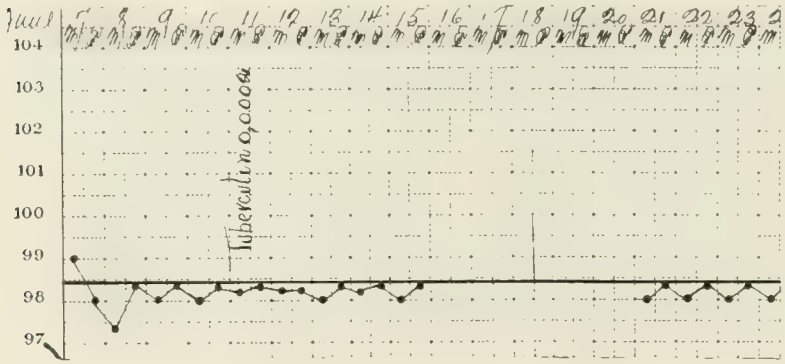

Chart No. 26.

reaction, and in the case shown in Chart 27, to which reference has just been made, I am sure no one would hesitate to call the reaction positive, although there is only one rise of temperature above normal, and this unaccompanied by any marked constitutional symptoms. In the case shown in Chart 28, after several rises to 99, the temperature goes to 99.2 after the seventh injection, and then there is no further rise even after 10 mg. In Chart 29 the temperature goes to 100 after the second dose and then there is no further rise. In Case 84 the temperature rises after 1 mg. to 100.5 and then no reaction to 5 mg. In Chart 19 it goes to 99.4 after the first injection. In none of these were there any constitutional symptoms or signs of a focal reaction, but the case, shown in Chart 19, showed a marked local reaction after the first dose. We have considered all four of these negative, although it must be admitted

that No. 19 possessed a certain grade of tuberculin hypersensitiveness. Möller[25] and Hammer[26] call attention to the frequent occurrence of such slight temperature rises after the first doses of tuberculin and they, too, consider them negative if there is no rise to subsequent higher doses. The case shown in Chart 20 shows no febrile reaction and no constitutional symptoms, but a marked local reaction after the first and second dose. This case, too, we have considered negative although there must have been some hypersensitiveness. The patient whose case is shown in Chart 30 had an old tuberculous knee with cough and indefinite pulmonary signs. She gave the most marked local reactions of any case in our series, each injection being followed by a large tumor with swelling of the adjacent lymph glands. Oddly enough, the injections in the right side of the back were invariably followed by more marked swelling than those in the left. As the chart shows, there was never a marked rise of

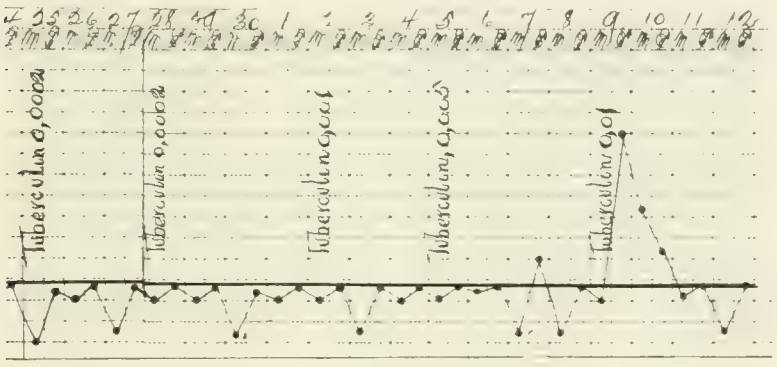

Chart No. 26—Continued.

temperature and there were only very slight constitutional symptoms. It is not easy to decide whether one should call such a reaction positive or negative. It gives some support to the view that local reactions with only slight fever and slight constitutional symptoms indicate healed rather that active lesions. Chart 31, too, presents difficulties in interpretation. Constitutional symptoms were present only after 10 mg. There was a marked local reaction after the fifth and ninth injections. The case shown in Chart 32 illustrates the irregular type of reaction which often occurs in advanced pulmonary tuberculosis. There is more of a general increase in the fever variations associated with signs of a marked focal reaction than an abrupt rise.

25. In Schroeder-Blumenfeld: Therapie d. Lungenschwindsucht, Leipsic, 1904.
26. Beitr. z. Klin. d. Tuberk., 1904, ii, 285.

THE DANGERS OF A TUBERCULIN REACTION.

Möller, Trudeau and other men of large experience assure us that when protected with reasonable caution the test has no dangers. There has, however, grown up in the use of tuberculin therapeutically a strong feeling that reactions are fraught with danger to the patient; and such a careful observer as Sahli refuses ever to produce a reaction purposely even to establish a diagnosis. Certainly in the two cases previously referred to the existing signs rapidly spread while diagnostic doses of tuberculin were being given and did not recede when the reaction subsided. It is true that these were definite cases of pulmonary tuberculosis and tuberculin was not needed to confirm the diagnosis, but they have impressed on us caution, and I feel strongly that tuberculin should be used as an aid in diagnosis only when our usual methods of investigation have failed to give a definite conclusion. This still leaves a field wide enough. One can not look with indifference on a reagent which may produce such

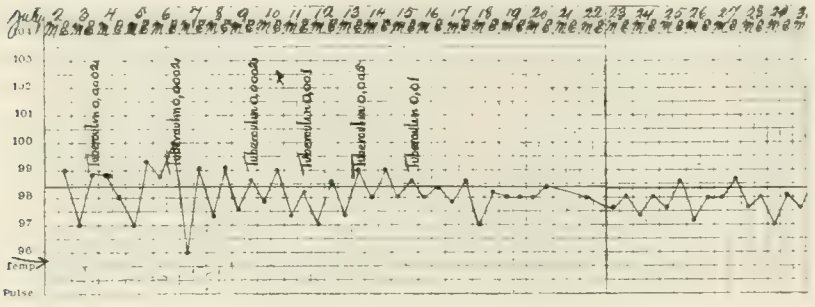

Chart No. 27.

intense constitutional symptoms and such prolonged periods of fever as in the instances we have cited. However, in none of our doubtful cases did any signs or symptoms remain which could be interpreted as permanent injuries from the use of tuberculin.

THE CLINICAL INTERPRETATION OF TUBERCULIN HYPERSENSITIVENESS.

A positive tuberculin reaction means tuberculin hypersensitiveness, and as veterinary practice has shown, tuberculin hypersensitiveness signifies a previous intimate contact with the tubercle bacillus. It is a notorious experience both in veterinary and in medical practice that animals with advanced tuberculous lesions fail to show tuberculin hypersensitiveness, for which we have already given a theoretical explanation; at any rate there is never any question of diagnosis in such instances, and in doubtful cases a negative tuberculin reaction means that the

patient has no active tuberculous lesion. Prolonged clinical observation of such negative cases has invariably lent support to this view, and while it need not theoretically be absolutely certain, practically it nearly approaches certainty. The interpretation of a positive reaction is by no means so simple. The statistics of Naegeli[27] and Burkhardt[28] show how wide the distribution of the tubercle bacillus is among human beings, and it becomes a matter for practical demonstration to show under what conditions these infected individuals show tuberculin hypersensitiveness. One is immediately struck, in looking at any large set of statistics of the tuberculin test, by the fact that so many individuals react. Beck[29] reports observations on 2,508 patients, and of these 1,525, or 60.8 per cent., react; 371 were definitely tuberculous and all reacted; 423 were suspected of having tuberculosis, and of these 364 reacted; 1,714 were convalescents or patients ill with other diseases, and none were suspected of having tuberculous lesions; 790, or 46.1 per cent., reacted.

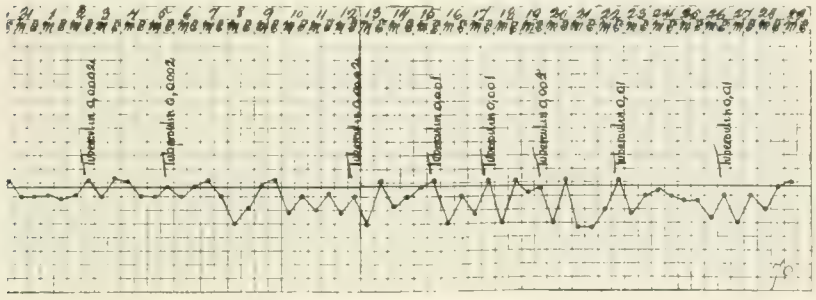

Chart No. 27—Continued.

These figures bear a striking resemblance to Burkhardt's statistics of 1,262 autopsies on adults. Tuberculous lesions were found in practically all and showed signs of activity in 62.5 per cent. Franz[30] injected 400 recruits of the Bohemian Army and 61 per cent. reacted. Fraenkel[16,24] reports 200 observations. Of 56 tuberculous cases all reacted; of 76 suspected cases 70 reacted; of 68 unsuspected patients 37, or 56 per cent., reacted. Of Bandelier's 500 suspected cases all but 37 reacted; of Hammer's 180, 164 reacted. Roth-Schultz reports, of 670 men 98.5 per cent. reactions, of 299 women 96.3 per cent. These patients all had

27. Naegeli cit. Burkhardt: Heft i, p. 139.
28. Ztschr. f. Hyg., liii. Heft i. p. 139.
29. Deutsch. med. Wchnschr., 1899, Nos. 5-9.
30. München med. Wchnschr., 1902, No. 7, p. 302.

symptoms or physical signs suggesting a pulmonary lesion. Of our 91 cases 11 were definitely tuberculous and all reacted, 75 were suspected cases and 63 reacted, 8 were patients with disease other than tuberculosis and 4 reacted. From these figures it is apparent, then, that about 90 per cent. of all suspected patients react and about 50 per cent. of patients with diseases other than tuberculosis, or individuals in whom no tuberculous lesion is expected. The objections that have been urged against the universal application of the anatomical records of Naegeli and Burkhardt may be applied with equal force here. The observations have been made for the greater part on general hospital patients, and perhaps the higher strata of society would give a lower percentage. This even seems probable, but we have no figures from which to judge, and it is scarcely to be

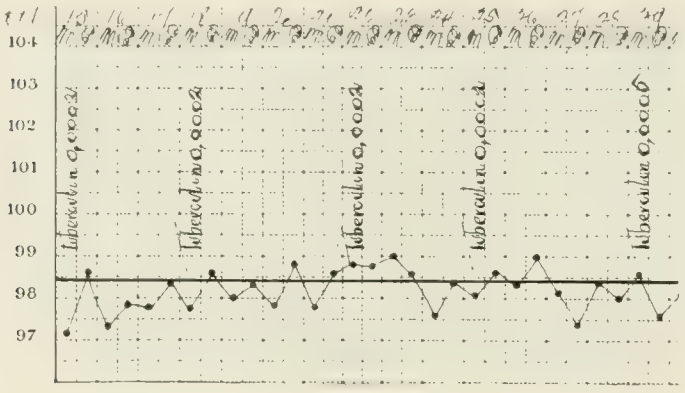

Chart No. 28.

presumed that they would be more than halved. This would still leave 25 per cent. of individuals without any clinical evidence of a tuberculous lesion presenting tuberculin hypersensitiveness.

There has grown up a widespread feeling of mistrust, or at least of suspicion, of sanitarium statistics. With the demand for the earliest possible cases of tuberculosis some have intimated that the evidence of diagnosis has been too lightly considered and many patients accepted in whom the presence of disease was, to say the least, doubtful. No one has been more conscious of such criticism than sanitarium physicians themselves, and they have made every effort to fortify their position. To get results in any way commensurate with the great expense of equipment and maintenance only early cases can be treated. No one would think of demanding the presence of tubercle bacilli in the sputum as the criterion for admission. Still we all know that the early symptoms of pul-

monary tuberculosis are often vague, the signs inconclusive and our judgment frequently faulty. Less than 50 per cent.[31] of the patients admitted to the German sanatoria have tubercle bacilli in their sputum. In the majority the diagnosis depends upon the skill and judgment of the physician in charge. Men of experience these are, and far from criticising their methods I most heartily support them. I believe firmly that the tendency is the correct one, and to achieve the best results let us treat a few cases that do not absolutely demand it, confident of the honesty of our aim and the general success of our method. Unfortunately the error in diagnosis is many hundred times on the side of conservatism to once on the side of radicalism. It must, however, be granted that in exceptional cases one man might offer a positive opinion where another

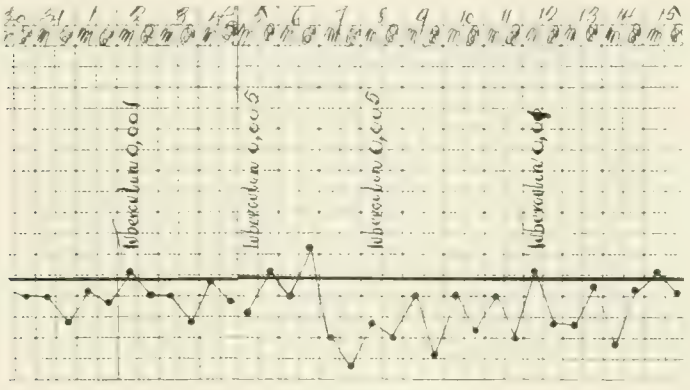

Chart No. 28 Continued

would express doubt and a third deny—and all three might be men of ability and experience. In a well-conducted sanatorium a certain number of such—let us call them questionable—cases must be admitted, and if tuberculin is to render us a service in diagnosis here is its especial field.

Now in justification of sanatorium records Bandelier quotes his results. Of 500 cases admitted to the sanatorium with symptoms or signs pointing to an early pulmonary tuberculous lesion, but without tubercle bacilli in their sputum, all but 37 reacted. This small percentage of error demonstrates glowingly, he thinks, that sanitaria treat and cure tuberculous patients. These 37 negative cases, however, had no clinical features by which they could have been distinguished from the 463 that reacted and would have been kept in the sanatorium and treated had

31. Pickert: Ztschr. f. Tuberkul., 1903, iv, 21.

tuberculin not been used. Certainly in our own cases a number of the patients that failed to react had far more definite symptoms and signs of tuberculosis than many that did react. If tuberculin did no more then differentiate 7.4 per cent. of Bandelier's cases, 9 per cent. of Hammer's and 16 per cent. of our own and stamp these definitely as not tuberculous it would still be well worth its use. What we take exception to is the attitude that a positive tuberculin reaction marks a patient not only as a suitable candidate for sanatorium treatment, but one urgently in need of it. In the view of our own experience and of the figures we have quoted we can not believe that tuberculin gives "absolute certainty" to a diagnosis or that it alone can place sanatorium statistics on an "irreproachable basis" (Bandelier). In speaking of a diagnosis we refer, of course, to a diagnosis of pulmonary tuberculosis, and let us add the qualifying adjective, *clinical* tuberculosis. As an example, a man comes complaining of pulmonary symptoms and the examination shows indefinite signs at one apex. He is given tuberculin. If he fails to react, our suspicion is dispersed. If he reacts we know that over 25 per cent. of patients without a suspicion of tuberculosis react, and in weighing the evidence I contend that we reach our conclusions more from a consideration of the symptoms and physical signs than from the tuberculin reaction. It adds a new bit of evidence to what we already have, and even an important bit of evidence, but it does not decide the diagnosis absolutely and indisputably mark the patient as a candidate for sanatorium treatment. It is of value only when viewed as a part of the general clinical picture and can not be compared in significance to finding tubercle bacilli in the sputum nor yet to such a characteristic symptom as a frank hemoptysis. It should be remembered, too, that when a patient reacts to tuberculin this is no assurance that the disease from which he is suffering is tuberculosis. Of our eight cases with diseases other than tuberculosis four reacted; one had arthritis deformans, one neurasthenia with abdominal symptoms and one bronchiectasis. The fourth case had a swelling of the wrist joint the diagnosis of which lay between tuberculosis and sarcoma. The patient gave a typical reaction to the first injection of 1/5 mg. of tuberculin. At operation the swelling proved to be sarcoma.

What we have said about the tuberculin reaction in relation to diagnosis has reference only to those cases in which no signs of a focal reaction are discovered. When a patient reacts to tuberculin and during the reaction a perfectly definite change is made out in the physical signs, the method becomes one of the most satisfactory diagnostic aids we possess.

We then know that the patient has tuberculosis, where he has it and something about its extent.

In our 75 suspected cases, then, we obtained positive information in 26, 12 being negative and 14 showing signs of a focal reaction. Surely these results alone would justify the use of the method. In the remaining 37 cases that reacted we formed our opinion only after full consideration of all the features. A number of them we felt sure were not pulmonary tuberculosis, and their future course has justified our opinion.

THE CLINICAL METHOD OF DEMONSTRATING TUBERCULIN HYPERSENSITIVENESS.

Koch's original method of giving tuberculin was to inject 1 mg., 5 mg. and then 10 mg., and if there was no reaction to repeat the last dose.

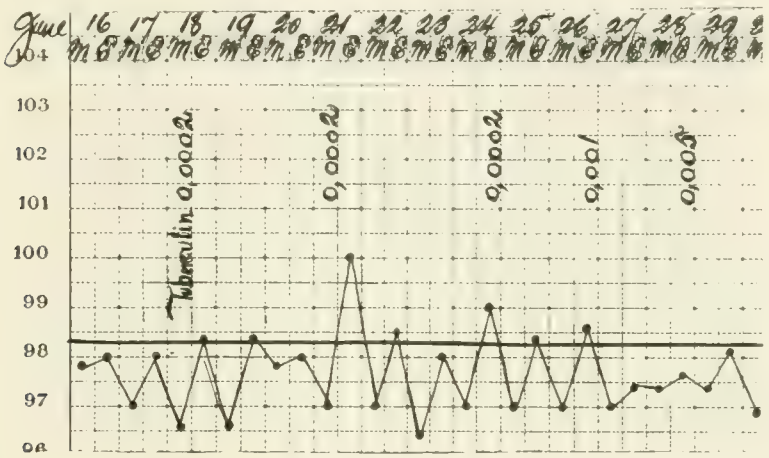

Chart No. 29.

Bandelier has advocated that this plan be strictly adhered to. Löwenstein developed the method of repeating small doses and has proposed the repetition of 1/5 mg. four times. As Raepke very justly objects, too many cases of early and definite pulmonary tuberculosis fail to react to this procedure to make it of satisfactory general application. In 28 of our cases that reacted small doses (less than one-half milligram) were repeated at least three times before ascending to larger; 15 reacted to such repetition, while 13 required higher doses; 5 of the 15 reacted to the first dose, 3 to the second, 2 to the third, 4 to the fourth and 1 to the fifth. Of the 13 requiring higher doses 8 had a small dose repeated three times, 3 four times, 1 five times and 1 eight times; 4 of the cases

that failed to react to the repeated small doses were definitely pulmonary tuberculosis. Repeated injections of tuberculin not only produce hypersusceptibility but they may under certain conditions bring about an obliteration of pre-existing hypersensitiveness. Just what these conditions are we do not know. I quite agree with Köhler, who emphasizes that we can never predict just what will follow an injection of tuberculin. We have no means of judging whether a patient will react to a small dose or to a large dose, mildly or severely. What we aim at is to begin a little below the minimal reacting dose and ascend gradually. No definite routine can be laid down to fit every case. We modify our method to suit conditions as they arise. I do not think there are ten cases in the whole series who have received injections just alike. At present our scheme

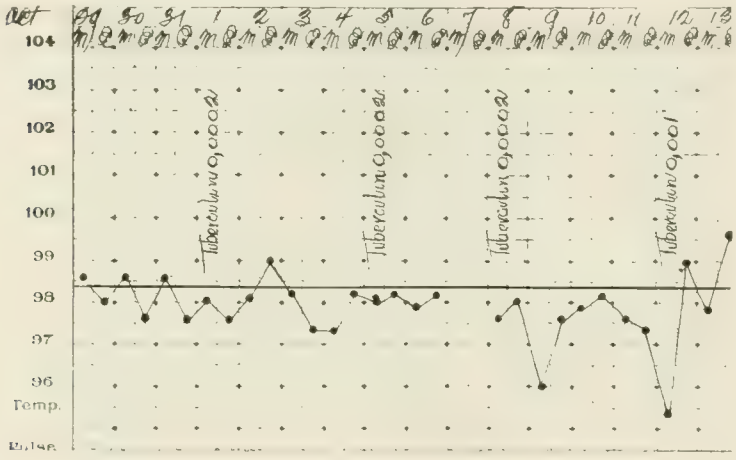

Chart No. 30.

is to give 1/5 mg., 1/2 mg., 1 mg. and 5 mg., but we seldom carry it out in such regular progression. Whenever a patient shows a tendency to react to a given dose, instead of following it with a larger the same dose should be repeated. In the cases shown in Charts Nos. 21, 33 and 34 the severe reaction might have been avoided had this rule been followed. It is, however, not of universal application, as Charts Nos. 35, 36, 37 and 22 illustrate. We begin with 1/5 mg. because we have found that it is exceptional for a patient to react to this initial dose. Of course occasionally patients will react even to much smaller doses, and Chart No. 38 shows a typical reaction to 1/1,000 mg. In children the initial dose should never be over 1/10 mg. and it is often best to begin with 1/20 mg. The terminal dose, too, should seldom be over 1 mg. This

question of the optional terminal dose has evoked much discussion. Koch makes 10 mg. the border beyond which even normal individuals may react; however, it would seem quite arbitrarily. Goetsch[32] insists that we must give 50 mg. to definitely exclude tuberculosis. We know that for healthy guinea-pigs there is no maximal dose, for they may stand as much as 20 c.c. without dying. There is no evidence to show that normal human beings are any more susceptible than guinea-pigs, but it is evident that there would be difficulty in establishing the point. It must be remembered that in using tuberculin we do not wish to discover trifling evidences of susceptibility, and as the results of the test are at best inconclusive it would seem that a restriction to moderately small doses would after all serve our purpose best. Raepke in a large number of cases got

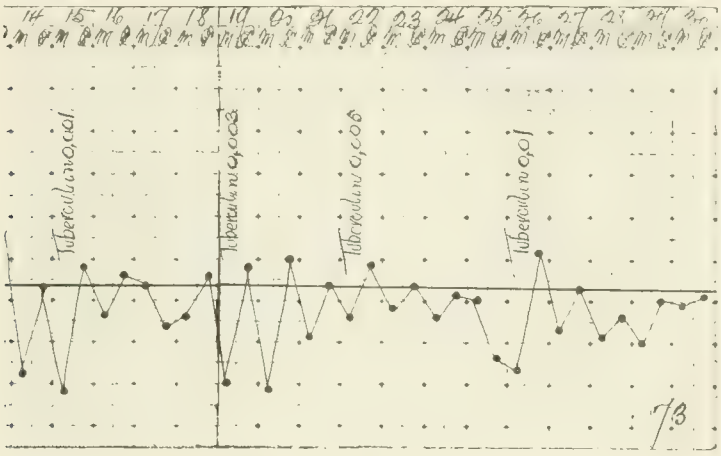

Chart No. 30—Continued.

as large a proportion of reactions with 5 mg. as he did with 10 mg. as the maximal doses. Turban,[33] Beck and Möller have shown that it is especially the early, fresh lesions which produce the most marked hypersensitiveness, and it is these cases particularly that we seek to recognize.

THE CUTANEOUS AND THE CONJUNCTIVAL TESTS.

During the past year two valuable contributions have been made to the use of tuberculin in diagnosis. Both of these methods depend upon the utilization of the local reaction as an index of tuberculin hypersen-

32. Goetsch. cit. Bandelier; see Note 5.

33. Turban: Beitrage zur Kentniss der Lungentuberkulose. Wiesbaden, 1899.

sitiveness without the production of fever, constitutional symptoms or a focal reaction. Von Pirquet[34] announced in May, 1907, that by putting a drop of tuberculin on the skin and making an abrasion through it most remarkable variations might be observed in the manner in which different individuals reacted. In the tuberculous patient the area becomes red in eight to twelve hours, then swollen and infiltrated, and in severe reactions vesiculation may occur. Occasionally the reaction may be delayed for thirty-six or forty-eight hours, when it is usually very mild; or it may develop a few hours after inoculation and rapidly subside. In a discussion of Von Pirquet's report, Wolff-Eisner stated that a similar reaction could be obtained by instilling a drop of tuberculin into the conjunctiva. Apparently quite independently Calmette made a similar observation and reported his method in June, 1907. The literature on

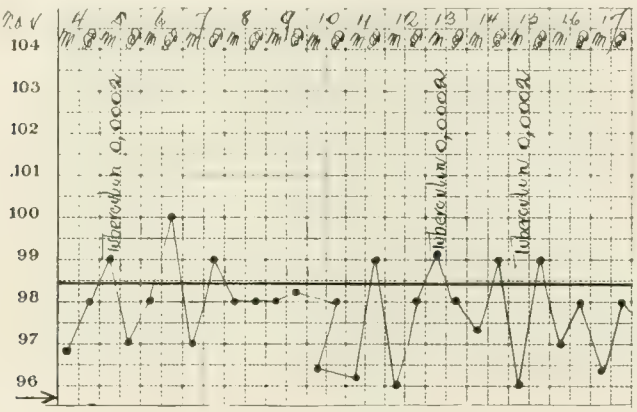

Chart No. 31.

these two reactions is already voluminous, but Wolff-Eisner[35] has collected it and given an exhaustive review of the results. During the past six months we have been using both methods for diagnosis, and although we are not prepared to give a detailed account of our experience I shall briefly refer to it. It is now generally conceded that, although the skin reaction is specific, it is too delicate a reaction to be of much service in diagnosis. Von Pirquet himself noted that nearly all adults reacted, and restricted the value of the method to early infancy. It is most interesting to see in his tables how the percentage of reactions steadily increases with advancing years: 0 to 4 months, 0 per cent.; 4 to 12

34. Berl. klin. Wchnschr., 1907, Nos. 22-23.
35. Beitr. z. Klin. d. Tuberk., 1908, ix, No. 1.

months, 10 per cent.; 1 to 3 years, 24 per cent.; 3 to 5 years, 37 per cent.; 5 to 8 years, 56 per cent.; 8 to 14 years, 60 per cent. Almost as many apparently healthy adults react as suspected cases. Of 360 tuberculous children, 88 per cent. reacted, the negative cases all being far advanced. In 100 autopsies on children from 1 to 14 years of age, 30 cases that had reacted all showed tuberculous lesions and 17 more had advanced or miliary tuberculosis that did not react. The other 54 cases were apparently free from tuberculosis and only one had reacted. In our earlier observations we placed a small drop of pure tuberculin on the skin of the arm and made a superficial abrasion through it. Secondary abrasions were made as controls on the bare skin or through a drop of 50 per cent. glycerin. We have never observed a reaction in any of the controls. Recently we have aimed to refine the methods by testing various dilutions

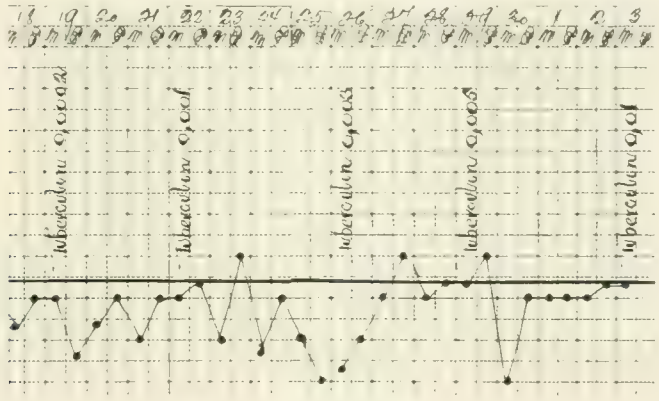

Chart No. 31—Continued.

from 1 to 20 per cent. In 137 observations by the older methods 60 cases were definitely tuberculous, 49 reacted, 11 did not. Of the 11 negative cases 9 were being treated with tuberculin and 2 were advanced cases. In 46 cases suspected of having tuberculosis, 26 reacted, 20 did not. In 11 cases of illness other than tuberculosis, 6 reacted, 5 did not; 2 had valvular heart disease, 1 lobar pneumonia, 2 neurasthenia, 1 ozena, 4 typhoid fever. Of 19 apparently healthy individuals, 14 reacted, 5 did not. These figures correspond closely with the average reports and illustrate that too many latent or insignificant lesions react for the method to be of much value in diagnosis unless the result be negative.

In performing the eye test Wolff-Eisner and most German observers use dilutions of old tuberculin varying in strength from 1 to 5 per cent.

To get rid of the glycerin and culture products Calmette precipitates old tuberculin with alcohol and dissolves the sediment in normal salt solution in strengths of from ½ to 2 per cent. Our own observations have shown us conclusively that glycerin in 1 per cent. solution will not cause any conjunctival irritation, and we see no reason why simple dilutions of tuberculin should not give results as satisfactory as the purified product. In our early observations we used a 1 per cent. and 2 per cent. solution of purified tuberculin furnished us by Dr. Baldwin of Saranac Lake; more recently, simple dilutions of old tuberculin. Our present routine is to instil a drop of measured volume of a 1 per cent. solution into one eye, if there is no reaction a drop of a 2 per cent. solution into the other, and if still no reaction after an interval of three to four days, another drop of a 1 per cent. solution into the first eye. Baldwin[36] and Smithies

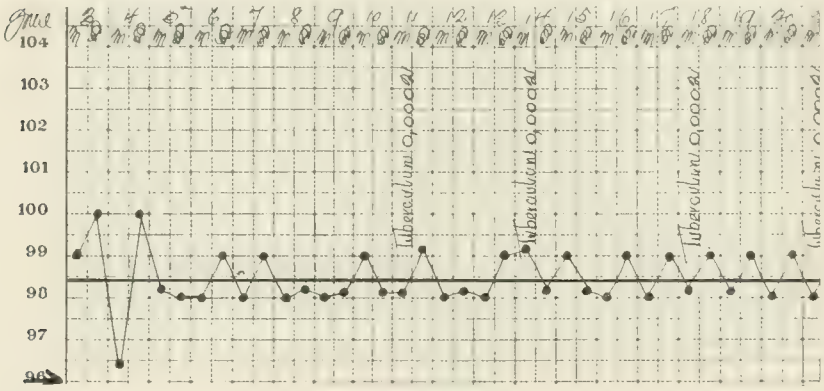

Chart No. 32.

and Walker[37] give elaborate details of the technic to be employed. We have observations on 104 cases in which the eye test was performed; 90 of these cases were also vaccinated, so the two methods may be compared.

Thirteen cases were diagnosed not tuberculosis. On the first instillation 11 were negative and 2 showed very slight reaction.

On second instillation one case which was slight, became positive and one which was negative became positive.

Five of the cases received a third instillation, 2 remained negative; 2 which had been negative became positive and 1 which was slight was again only slight.

Twelve of these 13 cases were vaccinated. In 4 the reaction was marked; in 6 slight and in 2 negative.

36. Jour. Am. Med. Assn., 1907, xlix, 1969.
37. Jour. Am. Med. Assn., 1908, l, 259.

Of the 4 cases with marked reaction, 1 reacted to eye slightly, one positively to third instillation, 1 on the second and 1 on the first.

Of the 6 cases with a slight reaction, 2 were negative to a single instillation, 1 negative to two instillations and 2 negative to three. One was positive on the second instillation.

Of the two cases with a negative reaction, 1 reacted positively to the second eye test, 1 was negative.

Twenty-four cases were definitely tuberculous.

First stage, 8 cases: Two positive to first eye test and 1 slight; 2 positive to second instillation; 2 negative to a single instillation and 1 negative to two. Two of the negative cases had tubercle bacilli in their sputum. All of the 8 cases were vaccinated. Six gave a marked reaction; 4 of these reacted to the eye test, 1 was slight and 1 negative. One gave a slight reaction; the eye was negative. One case was negative to vaccination and the eye test but had tubercle bacilli in the sputum.

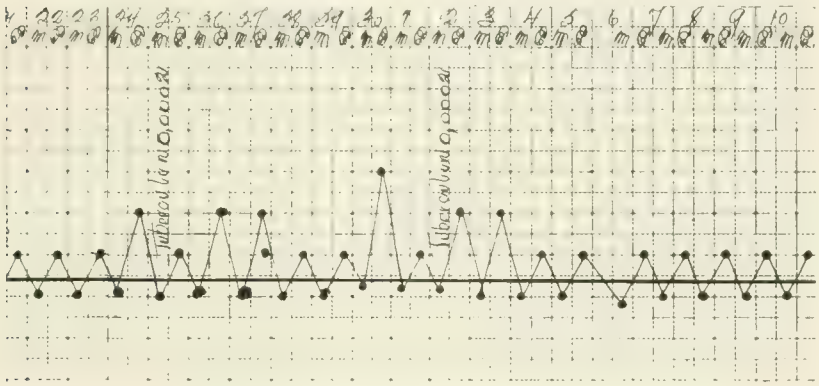

Chart No. 32 Continued.

Second stage, 5 cases: Three positive to first eye test and 1 negative; 1 was negative to 3 instillations. Vaccination: Four gave marked reaction; 1 was negative to vaccination and to all three eye tests.

Third stage, 9 cases: Two positive to first instillation and 1 slight; 1 positive to second instillation; five were negative, 3 to one instillation, 1 to two, and 1 to three. Eight of these cases were vaccinated. Five gave a marked reaction; 3 gave positive eye test; 1 slight and 1 negative. One gave a slight reaction; eye test slight. Two were negative to vaccination and to eye test.

An old, apparently healed pulmonary lesion showed no eye reaction to two instillations.

One patient with an old tuberculous knee and symptoms of an early pulmonary lesion gave a marked reaction to vaccination and to the first eye test.

Fifty-six cases were suspected of having pulmonary tuberculosis. Eleven gave a definite eye reaction, 4 to the first instillation, 2 to the second, and 5 to the third. Twelve gave a slight eye reaction, 4 to the first, 7 to the second, and

1 to the third. Thirty-three were negative, 17 to one instillation, 5 to two, and 11 to three. Of the 56 cases 54 were vaccinated. Twenty-four gave a marked reaction; 13 gave a mild reaction, and 17 were negative.

These figures show at a glance how much less frequent the eye reaction is than the skin.

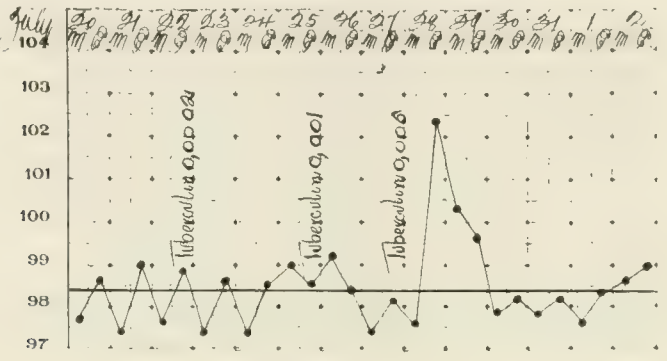

Chart No. 33.

Of 13 non-tuberculous cases, 2 gave a positive eye reaction, 10 a positive skin reaction.

Of 24 definitely tuberculous cases, 10 gave a definite eye reaction, 17 gave a definite skin reaction.

Of 56 suspected cases, 6 gave a definite eye reaction, 37 gave a definite skin reaction.

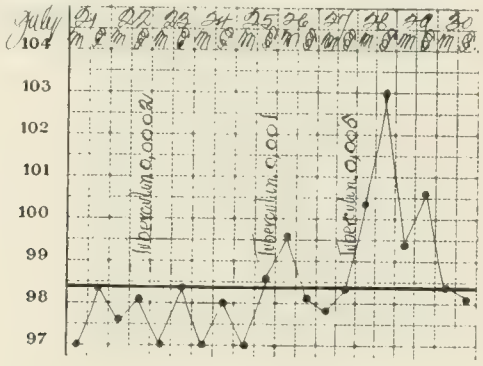

Chart No. 34.

In this summary it will be noticed that I have counted as positive neither the slight eye reactions nor those which became positive only after a third instillation. A slight reaction we have called one in which it was just possible to tell in which eye the drop had been put. The

reaction usually consisted in a little reddening or slight injection of the caruncle. Just what the significance of these extremely mild reactions is we are not yet in a position to say, and at least temporarily we are unwilling to class them as definitely positive reactions. As will be noted

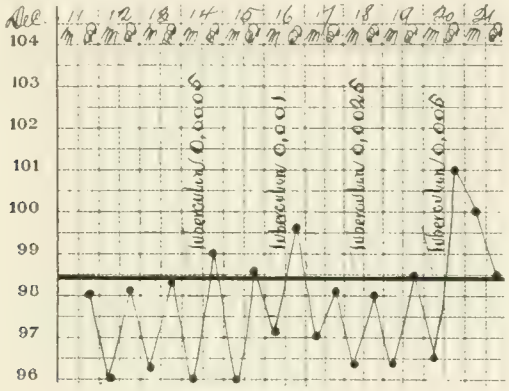

Chart No. 35.

from our figures, 17 suspected cases failed to react to an instillation in each eye, but 5 of these did react when a third dose was given. Now, this third dose was in nearly all instances only half as large as the second

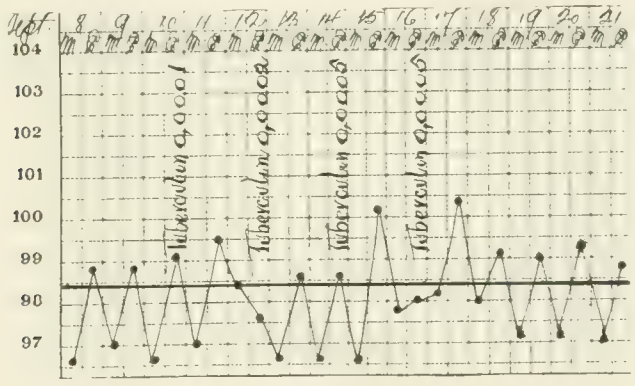

Chart No. 36.

dose, and the eye which at first gave no reaction showed most marked inflammatory changes after the second application. Evidently an application of tuberculin causes very remarkable changes in the local susceptibility to its influence. The effects are very similar to the general hyper-

susceptibility developed after the injection of small doses of tuberculin and the mechanism of the development of the two processes is in all probability the same. This reaction upon the instillation of a second dose into the same eye is such a frequent phenomenon that this feature alone

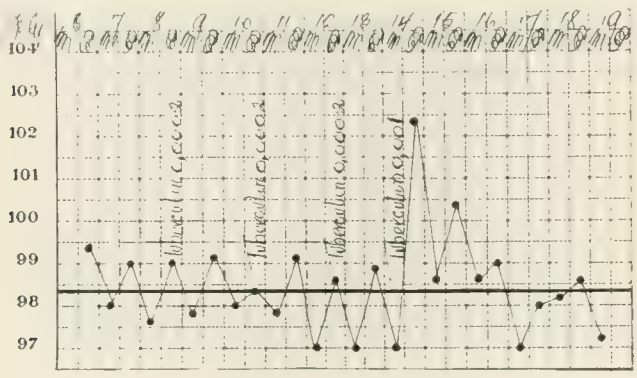

Chart No. 37.

would seem to contradict any relation to the opsonic index of the blood serum. Smithies and Walker consider these second reactions entirely accidental, depending on whether we instil at the crest of an opsonic wave

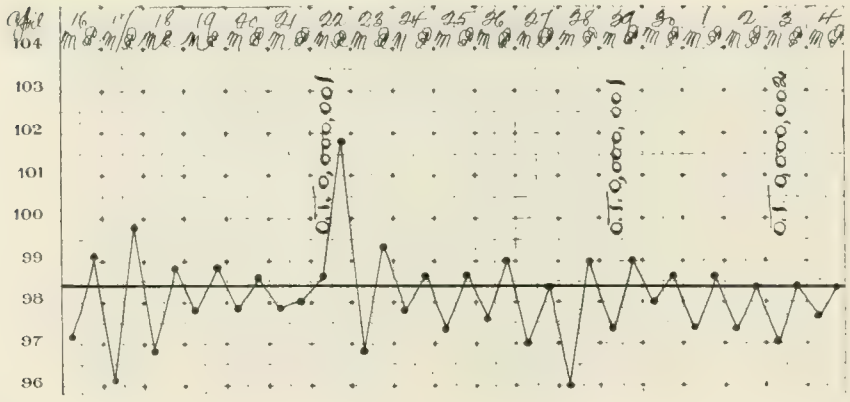

Chart No. 38.

or at the trough. Just what the clinical import of these second reactions is we as yet can not say. The general impression is that they should not be counted as diagnostic reactions. An interesting phenomenon of all local reactions is their tendency to flare up upon subsequent injections of

tuberculin. The case shown in Chart 39 gave an eye and skin reaction and was then put on diagnostic doses of tuberculin. When he reacted to 2 mg. the eye flared up, the points of vaccination become red and prominent, and each area of previous injection a little swollen.

We have then in the eye test a method of applying tuberculin which has at least a marked numerical advantage over the other methods. As our figures show, not nearly so many suspected cases react as to the injection method, but many tuberculous patients do not react and some apparently healthy individuals do. I may say that many observers present figures that are far more convincing than ours and run almost parallel with the clinical diagnosis. However, Wolff-Eisner, the introducer of the

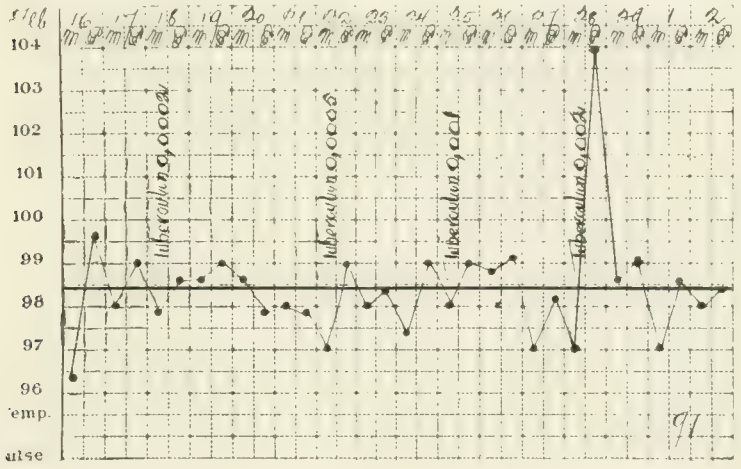

Chart No. 39.

method, reports results closely similar to our own. Only prolonged observation of tested cases will establish satisfactorily the value of the method.

SUMMARY.

To summarize these considerations we would say then that while tuberculin is a valuable aid in the diagnosis of pulmonary tuberculosis it must be used with care and the results interpreted with caution. We believe that the reaction is a specific one, but it must be borne in mind that a very insignificant lesion may produce tuberculin hypersensitiveness and the prevalence of such lesions should be fully realized. A negative reaction we consider decisive information, as is also a focal reaction. In the absence of a focal reaction tuberculin hypersensitiveness

must be viewed as one phase of the clinical picture and our judgment not be too much warped by its presence. As a clinical procedure no routine schema can be advised, as we must alter our method to meet conditions as they arise. For adults some such scale as 1/5, 1/2, 1 and 5 mg. may be suggested; for young children 1/10, 1/5, 1/2 and 1 mg. The cutaneous reaction is too delicate an indicator to be of any value in diagnosis unless the reaction be negative, which it seldom is in adults. The eye reaction gives results more nearly in accord with clinical experience, but by no means absolute certainty. We do not feel that it can supplant the subcutaneous method. It will be well for some time to use the two together, but not simultaneously. The eye inoculations should precede the subcutaneous by at least a few days.

AN EXPERIMENTAL AND CRITICAL STUDY OF THE ETIOLOGY OF CHRONIC NEPHRITIS.*

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NEW YORK.

"It is only when the full etiology of disease is known that the medicine of our day can become the medicine of the future—that is to say, hygiene in its widest sense."—PAWLOW.

CONTENTS.

Introduction—Methods—Selection of material—The effect of alcohol, ether, chloroform and amyl nitrite inhalations—The effect of injury of the kidney by the hypodermic needle, and of normal saline solution, adrenalin and alcohol solutions injected directly into the renal parenchyma—The effect of adrenalin and gelatin solutions injected directly into the veins—Summary of experimental results—Discussion on the etiology of chronic nephritis—Conclusions—Bibliography.

INTRODUCTION.

With the knowledge that the combined death rates from heart and kidney diseases have almost doubled within the past twenty-five years in the cities of Boston, New York and Chicago,[1] there has been offered no sufficient explanation for the cause of this increase, or of the widespread occurrence of nephritis, and no means of prevention are proposed offering any hope that the increase will be checked in the future. Without knowledge of the cause of disease, little of permanent value has ever been done toward its prevention, if one might except the discovery of vaccination for the prevention of smallpox.

While a variety of substances have been used successfully to cause diseased conditions in the kidneys of animals, such as mineral or vegetable poisons or irritants, the toxins of pathogenic bacteria, and nephrotoxins, at present the lesions reported and the conditions created can not be claimed to resemble essentially the lesions of chronic productive nephritis in man, which are found so frequently at autopsy that a normal kidney is a rare exception in an adult.

Recognizing that the accepted etiologic factors mentioned and copied from author to author, from the time of Richard Bright, account for many of the frankly-marked cases which can be followed in an almost unbroken chain of clinical and pathologic evidence from the inception

* Work done under the auspices of and aided by a grant from the Rockefeller Institute for Medical Research in the laboratories of physiology and pathology in the College of Physicians and Surgeons, Columbia University, New York.

1. Darlington: New York Med. Jour., 1907, lxxxv, 1158.

of the disease until death, there remain unexplained the causes of cases of so-called initial nephritis. Chronic inflammatory processes in the kidney are so commonly found at autopsy when there has been no reason to suspect nephritis before death,[2] that we must add many cases of unrecognized nephritis to those which are recognized but which lack sufficient etiologic explanation.

While a variety of causes are known to be responsible for, or to contribute to, the occurrence of chronic interstitial or productive inflammation in various tissues, circulatory disturbance resulting in a stagnation of venous blood or a diminution in the supply of arterial blood, or both, is an almost constant accompaniment, and may in some instances be shown to be the sole cause of the accumulation of connective tissue to the permanent and increasing detriment of the functional activity of the tissue or the organ involved.

The means at our disposal to effect changes in the blood supply of the kidney are few and offer many obstacles in the way of drawing accurate conclusions. The facts given here are based on experimental conditions produced in fourteen dogs over a period of twenty-six months, the plan of tests and observations being outlined in the preceding summary.

METHODS.

Small and medium-sized dogs were used for the experiments. It was found necessary to test the urine of dogs selected, over a period of three months, to eliminate those in which occasional or persistent albuminuria indicated a probable spontaneous or rather existing nephritis of unknown origin.[3] During this period of probation the dogs were kept in large cages, where they had full freedom of movement, and from which they were released at least every second day to run about for a short time, either in the building or in the yard outside. Their diet during this period was water and Spratt's dog biscuit. In selecting the fourteen dogs that were finally used, eleven were rejected because of albuminuria. The prevalence of albuminuria in dogs used for experimental purposes and the need of care in selecting material has been noted by Pearce[3] but so far as I can find there is no mention of such precautions being taken by any other experimenters with dogs or other animals. Inasmuch as removal of a piece of the kidney for diagnostic purposes, before the tests are begun, does not give reliable information as to an existing nephritis, and, moreover, as such a procedure, as will be shown later, tends to the production of such lesions as are being sought for by other

2. Emerson, C. P.: Jour. Am. Med. Assn., 1906, xlvi, 5, 89.

3. Pearce: Univ. Penn. Med. Bull., 1903-4, xvi, 217.

means, we must rely on the urinary examinations as the best, though certainly not a perfect, test for the presence of a nephritis. As Pearce[3] has shown, and as will be shown in the following tests, nephritis may exist in dogs without albumin or casts being constantly or at any time present in the urine.

The dogs that were finally selected were kept continuously on the diet described above, with occasional changes to meat diet, for periods of a week or two every six months. All but three of the dogs suffered from mange at one time or another while they were under observation, and most of them recovered completely from it by the application of 10 per cent. sulphur ointment to the skin. Several of the dogs had attacks of diarrhea, which were checked by a dose of castor oil and a diet of milk.

Three classes of test procedures were used: (A) inhalations, (B) hypodermic injections into the kidney substance, and (C) hypodermic injections into the veins or the muscles of the legs.

(A) INHALATION METHOD.

Alcohol, ether, chloroform and amyl nitrite were used to see if the repeated use of general vasodilators would produce any appreciable changes in the functions or structure of the kidney. The dog was placed in an air-tight wooden box, provided with two glass windows in the top, and an entrance tube for air at one end connecting directly with the supply flask, and an exit tube for air at the other end, provided with a mica valve so adjusted as to prevent the entrance of air, but allowing air to pass out when the pressure in the box was only slightly over atmospheric pressure.

The supply flask was connected by a one-half inch rubber tube with the entrance tube of the box by one opening, and to the tube of an artificial respiration apparatus by the other opening. A third and very small tube, with a stop-cock, in the cork of the supply flask allowed of the administration of the desired amount of the drug to be used. The flask was immersed in a pail of water, which was kept at a temperature of from 30° to 35° C. during alcohol administration, and at from 17° to 20° C. when ether, chloroform and amyl nitrite were being given.

Air was supplied by an artificial respiration apparatus at the rate of 35.5 respirations a minute, and each inspiratory blast had a volume of 400 c.c. Thus the dogs were supplied with 14,200 c.c. of air a minute. As the air passed into the supply flask and out of it into the box it carried with it some of the vapor of the drug to be administered. Knowing the time taken in evaporating the volume of the drug put into the supply bottle, and the amount of the drug and of the air supply being known.

it was found that the percentage of the drug present in the air which the dog breathed was as follows:

For alcohol during 30 minutes	.01765	per cent.
For ether during 30 minutes	.03521	per cent.
For chloroform during 30 minutes	.007	per cent.
For amyl nitrite during 15 minutes	.0018	per cent.

There was little or no struggling of the animals in the box, as the administration of the drugs was gradual, and after a few treatments the dogs usually kept perfectly quiet and relaxed on the floor of the box.

The respirations and the color of the nose and lips could be watched through the windows in the box, and indications of failing circulation were met by opening the box or by connecting the air supply tube directly with the entrance tube of the box, cutting out the supply flask from the circuit. Squibb's ether, and chloroform, and amyl nitrite were used, and absolute alcohol was used. After the treatment was finished the dog was allowed to recover gradually from the effect of the drug, and when muscular co-ordination was restored he was taken to the cage again.

(B) HYPODERMIC INJECTIONS INTO THE KIDNEY SUBSTANCE.

The skin was shaved over the lumbar region on the left side and then washed over with 95 per cent. alcohol. The kidney was then fixed as well as possible with one hand, and a long hypodermic needle was passed through the skin and lumbar muscle until the kidney was felt. The needle point was then passed through the capsule and the dose of the drug injected. This procedure was not always successful, but tests on the cadaver, and on many dogs which were used for other purposes, and observed with the kidney and needle *in situ,* make me feel confident that the majority of attempts were successful.

To control these tests two dogs were used in which no drug was given. In one the needle was simply inserted into the renal parenchyma and withdrawn, and in the other 6 c.c. of normal saline solution were injected into the kidney substance. The alcohol and adrenalin chlorid solutions were used to test the possibility of affecting the blood supply of the kidney locally without injuring the parenchyma primarily. The alcohol was used in 25 per cent. strength in normal salt solution, and the adrenalin chlorid was used in 1 to 1,000 solution.

(C) INTRAVENOUS INJECTIONS.

The veins of the leg were used and aseptic precautions were observed. A 10 per cent. aqueous solution of acetate of lead was used to obtain a standard type of chronic toxic nephritis. A 1 to 1,000 solution of

adrenalin chlorid was used to see if general vasoconstriction would produce any secondary results in the kidney. A 5 per cent. solution of gelatin in water, which was fluid at body temperature, was used to test the effect of persistently increased viscosity of the blood upon renal function and structure, the gelatin being injected through a warmed syringe with a small aspirating needle.

URINARY TESTS.

The urine was collected at intervals during the course of treatment, the dog being kept in a metabolism cage for a day or two for the sake of obtaining a clean sample of urine. The urine was tested as to its specific gravity, for albumin by the use of heat and nitric acid, and microscopically for casts. It may be properly noted here that casts were not found in any case.

HISTOLOGIC MATERIAL.

At the autopsy specimens of the various organs were hardened in equal parts of Mueller's solution and 5 per cent. formalin and were later washed, imbedded in celloidin, sectioned, stained in hematoxylin and eosin, and mounted in balsam.

A. *EFFECTS ON THE KIDNEY OF REPEATED GENERAL VASOMOTOR DILATATION.*

ALCOHOL.

In spite of the disagreement among physiologists and among clinicians as to the position alcohol holds in nutrition, there is substantial agreement as to its effect on the circulation. The best summary of results is found in the recent observations of W. E. Dixon,[4] who reaches the following conclusions.

"Alcohol does not affect all the vessels in the intact animal in the same way.

"Alcohol dilates the vessels of the skin rapidly, and tends to constrict the vessels in muscle tissue, and to a less marked degree in the splanchnic area, large doses causing immediate splanchnic constriction.

"The usual effect in man is a central one, causing superficial dilatation and internal constriction. This is the reaction of the organism against the rise of temperature which the increased metabolism would otherwise result in. Central stimulation (or stimulation of the corpus striatum) causes increased metabolism.

"The sum total of general pressure changes due to alcohol is usually a vasodilatation."

4. Dixon: Jour. Physiol., 1907, xxxv, 346.

We may suppose, therefore, that the frequent administration of alcohol to an animal would subject the kidney to fluctuations in its vascular supply. Periods when there was a decided decrease in the blood bulk passing through the kidney, owing to a lowered general pressure and construction of the splanchnic vessels, would result.

PROTOCOL 1.

Dog.—White male fox terrier; weight, 8290 G. Urine, free from albumin and casts; specific gravity, 1013. Diet, dog biscuit and water. Probation period, July 1 to Sept. 15, 1905. Normal respiration and pulse at rest, 20 and 100.

Alcohol was administered by the inhalation method at intervals of a few days from Sept. 5, 1905, to March 17, 1906, the doses varying from 25 c.c. to 60 c.c., and the total amount of absolute alcohol used being 700 c.c. The duration of muscular incoordination averaged two hours at each administration. A marked and unexpected result of this method of administering alcohol was the extreme rapidity of respiration and the change in the pulse-respiration ratio. At the height of the effect, usually at the end of fifteen minutes, the respirations increased to from 220 to 260 a minute, and when on several occasions the dog was removed from the box for better observation of this phenomenon, the pulse was found to be from 120 to 130 a minute, the respirations remaining at 220 or more. This was in no way to be mistaken for dyspnea, as the tongue and nose were pink and the rapid respirations persisted for some minutes after the dog was removed from the inhalation box. Furthermore, neither this dog, nor the others tested in the box, showed any evidence of dyspnea when supplied with air alone, and in all probability this was a manifestation of excessive central irritation.

March 17, 1906: Weight, 9,300 G.; appears in good condition, has had no mange; urine contains marked traces of albumin, specific gravity 1020. April 28, 1906, the dog died, having had general muscular spasms several times a day for the past week; death in tonic convulsion; weight, 7940 G.

Autopsy.—No edema of the body, but dilatation of superficial capillaries; no fluid accumulations in the pleura, pericardium or peritoneum. Heart distended and enlarged. Lungs deeply congested. Kidneys soft, swollen and congested.

Histologic Examination.—The heart muscles and aorta show no changes from normal structure. The lungs show intense engorgement with a few areas of pneumonic consolidation in what would correspond to the stage of red hepatization. There is no connective tissue increase in the lungs. The liver cells are poorly defined, take the stain poorly, and there are a few small areas of necrosis in the parenchyma. There is no increase in the connective tissue. The kidneys present the picture of severe chronic degeneration. The capsule is much thickened and there is an extension of the recently forming new connective tissue from the inner layers of the capsule into the cortex of the kidney. Here we find compression of the superficial tubes. The glomerular tufts are, for the most part, distended and the tuft cells increased in number. Elsewhere the glomeruli share in the general parenchymatous degeneration. It is difficult to find any normal tubules, straight or convoluted. The degeneration has not been of sufficient duration to allow of replacement fibrous formation, although small areas of round-celled connective tissue are found in the cortical layer.

ETHER.

The vasodilatation caused by ether is one of its marked effects on the vascular system, and its repeated use might be expected to cause some injury to the function of various tissues, as the result of the general low-

ering of blood pressure, apart from the accepted irritant effect it has upon the kidneys and lungs during and immediately after its administration.

PROTOCOL 2.

Dog.—Black and white male fox terrier; weight, 6100 G. Probation period from April 28, 1905, to Sept. 9, 1905. No albumin or casts in the urine; specific gravity ranged from 1028 to 1038. Respirations from 20 to 24, pulse from 90 to 100. Ether was administered by inhalation method at frequent intervals from Sept. 9, 1905, to March 24, 1906, the doses varying from 90 to 200 c.c., and the total amount used being 5590 c.c. The duration of the effect of the drug in each instance was from 20 to 60 minutes. The pulse was increased from 180 to 200, and the respiration to from 36 to 44 in the minute. Cyanosis did not occur, and the skin, though warm and pink, did not show any marked vasodilatation during treatment.

March 24, 1906: Weight, 7340 G.; in perfect condition; no albumin or casts in the urine.

Feb. 22, 1907: During the past year the dog has been in uniformly good condition, on the diet as described; no albumin or casts have been found in the urine; weight 7210 G.

July 19, 1907: Still in the best of condition; weight 7210 G.; no albumin or casts; killed by destroying medulla with a knife, i. e., by "pithing."

Autopsy.—No abnormal appearances in any organs.

Histological Examinations.—Heart, liver and aorta present no abnormal microscopic appearances. The kidneys show a marked chronic inflammation, characterized by moderate thickening of the capsule in a few places, with a slight increase of connective tissue cells from the surface of the capsule into the cortex of the kidney, and a free subcapsular vascular network. The cells of the glomerular tufts are increased in size and number, and the capsular cells are in some instances increased. There are numerous small areas of connective tissue of comparatively recent formation, and in no instance have they resulted in contraction of the tufts after a resulting atrophy. The tubular epithelium is swollen, but not degenerated. The appearance would suggest a chronic productive nephritis, resulting from chronic congestion.

CHLOROFORM.

Chloroform inhalation causes a fall in general blood pressure and, according to Thompson,[5] an increase of blood flow through the glomeruli of the kidney, a prolonged administration resulting in a vascular stasis in the glomerular vessels. In other words, aside from its effects as a protoplasmic poison, which chloroform has on all tissues, it causes a general low blood pressure throughout the body, and a greater or less congestion of the kidney according to the depth of the narcosis. Embley and Martin[6] explain the effect of chloroform inhalation from 1 to 3 per cent. vapor as due to a paralysis of the neuromuscular mechanism of the renal vessels, which they say accounts for most of the fall in general blood pressure always noted in chloroform narcosis.

5. Thompson: Brit. Med. Jour., 1906, i, 608.

6. Embly and Martin: Jour. Physiol., 1905, xxxii, 147.

PROTOCOL 3.

Dog.—Brown and white male fox terrier; weight, 6400 G. Urine, specific gravity, 1024; no albumin or casts. Normal respiration, 22; pulse, 90. Probation period from April 28, 1905, to Sept. 16, 1905; mange during the summer, cured by September 16. Chloroform was administered by inhalation from Sept. 28, 1905, to March 24, 1906, at frequent intervals. The dose varied from 30 to 40 c.c. at each treatment, the total amount used being 1280 c.c. The duration of the effect of the drug varied from 45 to 75 minutes at each treatment; the pulse was increased to 96 or 100; respiration decreased to 12 or 14 in a minute. Occasionally it was necessary to use artificial respiratory movements, with the dog removed from the box, to accomplish resuscitation from the occasional collapses, which the free use of chloroform sometimes brought on.

Feb. 1, 1906: Weight, 6770 G. Appears to suffer from some urinary irritation. Urine, specific gravity, 1044; heavy traces of albumin.

March 24, 1906: Weight, 8050 G. In fine condition; urine free from albumin and casts; specific gravity, 1055.

Nov. 22, 1906: Died; weight, 6040 G.; had been failing in strength for some time past; no mange. Except for an apparently enlarged heart there is nothing noticeable at autopsy except marked emaciation.

Histologic Examination.—Heart muscle, aorta and liver normal. Lungs show considerable collections of black granules surrounded by connective tissue. Many of the alveolar cells include foreign particles. The kidneys show swelling and hypertrophy of the tuft cells and some proliferation of the capsular cells about the glomeruli. The kidney capsule shows no changes. The tubules show a moderate cloudy swelling, and the lumen in some instances is filled with granular detritus. There is no new connective tissue formation.

AMYL NITRITE INHALATION.

Amyl nitrite acts directly on the muscular coat of the blood vessels and causes a wide dilatation. The formation of methemoglobin, which occurs rapidly, prevents the use of amyl nitrite over long periods and was the cause of death in one of the tests to be described. It was thought probable that repeated alterations in the general blood distribution of the body, caused by amyl nitrite, might affect the kidneys.

PROTOCOL 4.

Dog.—Brown and white male fox terrier; weight 7050 G. Urine, specific gravity, 1030; no albumin or casts. Normal respiration, 16; pulse, 96. Probation period from May 24, 1905, to Sept. 11, 1905. Amyl nitrite was administered at intervals from Sept. 11, 1905, to Feb. 6, 1906, in doses of from 2 to 7 c.c. each, the total amount used being 170 c.c., the effect lasting from 20 to 40 minutes. Vomiting, dizziness and apparently delirium occasionally accompanied recovery from the use of the drug.

Feb. 4, 1906: Urine free from albumin and casts; specific gravity 1050; weight, 6730 G.

Feb. 6, 1906: After being in the box ten minutes with a dose of 4.5 c.c. the dog collapsed and could not be resuscitated from the extreme cyanosis and urgent dyspnea which shortly terminated in death.

Autopsy.—This revealed a blanched surface, deep (methemoglobin) cyanosis of mucous membranes, muscles pale and purplish red, heart intensely engorged, lungs collapsed and pale, liver deeply congested, kidneys tense and deeply congested, stomach and bowels empty.

Histologic Examination.—The heart and lung specimens were spoiled in the hardening fluid and could not be cut. The liver shows general capillary distention and engorgement. The two kidneys appear intensely congested. The glomerular tufts are distended with blood. The tubules almost uniformly are separated from one another by capillary vessels full of red blood cells instead of appearing to be in direct contact which is usually the case, i. e., the entire capillary network of the kidney appears engorged without any change in the parenchyma or capsule. There is no new connective tissue formation. This picture of acute congestion would certainly be expected from the cause and manner of death.

PROTOCOL 5.

Dog.—White and brown mongrel male, 8350 G.; no albumin or casts in urine; specific gravity 1014. Probation period from June, 1905, to Nov. 4, 1905. Amyl-nitrite was administered from Feb. 8, 1906, to March 24, 1906, in doses of 3 c.c. each to a total of 50 c.c. The effects were similar to those observed in the dog of Protocol 4.

Feb. 26, 1907: Weight 8940 G.; trace of albumin, general condition good.

July 1, 1907: Weight 7500 G.; dog died after a period of gradual failure of appetite and nutrition without convulsions or other appearances of disease.

Autopsy showed no gross evidences of disease except an unusually flabby heart muscle and congested lungs.

Histologic Examination.—The heart, liver and lungs are normal. The kidneys show moderate thickening of the capsule, but no tendency to connective increase or the formation of wedges in the kidney parenchyma. There is distinct, though not extensive increase in the glomerular tuft cells, and in a few instances a flattening or atrophy of the capsular cells. The tubules are in some places markedly degenerated as shown by the granular and non-nucleated condition of the cells, the abundant granular detritus in the lumen, and the absence of clearly defined cell outlines. A few areas in the outer layer of the cortex show young round celled connective tissue formation.

SUMMARY A.

1. The inhalation of alcohol has caused chronic degeneration of the kidneys with a beginning connective tissue replacement.

2. The inhalation of ether has caused a chronic productive nephritis, in which we find a swelling of the tubular epithelium, increase in the size and number of the glomerular tuft cells and areas of connective tissue formation.

3. The inhalation of chloroform has caused some interference with the nutrition of the glomerular and tubular cells, resulting in a moderate swelling and degeneration.

4. The inhalation of amyl nitrite has caused in one instance death with marked visceral engorgement and intense renal congestment, and in another instance we observe a moderate degeneration of the tubular epithelium and a connective tissue formation.

5. The three dogs which had been subjected to alcohol, chloroform, and amyl nitrite inhalation a considerable time before their death, died under such conditions as to make one suspect an error in nutrition and elimination, and the pathologic findings, although not conclusive, sug-

gest that the condition of the kidneys was probably responsible for their deaths.

6. The facts that the four dogs, which survived the prolonged treatment by inhalation of the various drugs, gained in weight and maintained apparently excellent health up to the time the treatment was discontinued, and that the symptoms of failure in nutrition occurred some months later, argue for the probability that none of the drugs caused acute degenerative changes at the time of their administration, as they are known to do when given in large doses, but that the repeated disturbances of circulation which all these drugs effect resulted finally in the various grades of chronic degeneration, followed or not by chronic productive nephritis, which were found at autopsy.

B. EFFECT ON THE KIDNEY OF MECHANICAL INJURY OF ITS SUBSTANCE AND OF VARIOUS DRUGS INJECTED DIRECTLY INTO ITS SUBSTANCE.

ALCOHOL.

Alcohol was used in two dogs, in one in 50 per cent. strength and in the other in 25 per cent. strength, with the expectation that a coagulation of the kidney substance might occur at the site of the injection, which would so interfere with the nutrition of the kidney that a general nephritis would result.

PROTOCOL 6.

Dog.—White and black male fox terrier, weight 9110 G. Urine free from albumin and casts throughout a four-month probation period as described above. Between January 11 and 31, 1906, ten injections of 50 per cent. alcohol of 4 c.c. each were made into the left kidney. No albumin was found in the urine of this dog at any time.

Feb. 8, 1907: The dog died, weight 5880 G.; it had been failing in strength for some time past although taking large amounts of biscuits and water and not suffering from diarrhea or vomiting. No convulsions.

Autopsy.—Emaciation severe; right kidney pale, smooth, normal; left kidney deep purple, scarred and intimately adherent to the lumbar muscles. The heart, aorta, liver and lungs appear normal.

Histologic Examination.—The heart, aorta and liver appear normal. The lungs show slight capillary congestion. The right kidney has a normal capsule and parenchyma. The left kidney shows advanced and extensive, chronic inflammation, most severe at the point of dense renomuscular adhesions and extending in a wide area of obliterating connective tissue growth as deep as the pelvis of the kidney. In these regions, of which there are several, extensive destruction of the glomeruli and the tubules has occurred. Hyaline and granular material fills the tubules, the tubular epithelium being represented in many cases by a shrunken nucleus and a slender layer of cell bodies. The fibrous tissue is organized and dense, and what vessels have originally taken part in the active process of repair are now sharing in construction and obliteration, as in scar tissue. The kidney presents all stages of advanced productive nephritis, apparently as the direct result of the coagulation infarct which must have resulted at the time of the injection of alcohol into the kidney substance.

PROTOCOL 7.

Dog.—White and black fox terrier, female; weight after three months' probation period 9850 G. Urine, free from albumin and casts, specific gravity 1024. From Feb. 2 to Feb. 27, 1906, the dog received ten injections into the left kidney of 6 c.c. each of 25 per cent. alcohol.

Dec. 20, 1906: Weight 6300 G.; the dog has been failing for past four weeks, appetite is poor and diarrhea is present, lately increasing to general convulsive seizures.

Dec. 24, 1906: Died. Weight 6000 G.

Autopsy.—Lungs show hypostatic congestion at the bases; the heart and vessels appear normal; right kidney normal; left kidney adherent to lateral abdominal wall; kidney substance appears normal.

Histologic Examination.—Heart and liver show no variations from normal. Right kidney appears normal. Left kidney shows moderately thickened capsule and a few areas of connective tissue infiltration from the capsule inwards. There is no degeneration or inflammatory process throughout the kidney parenchyma.

ADRENALIN.

Adrenalin was used in one dog in the expectation that some distinct difference between the resulting constriction of vessels locally and the effect of alcohol on the kidney might appear.

PROTOCOL 8.

Dog.—White female mongrel; weight 7150 G. No albumin or casts found after four months' probation period. Between Jan. 11, 1906, and Feb. 27, 1906, nineteen injection of 3 c.c. each of adrenalin chlorid solution (1 to 1000) were given into the left kidney.

April 18, 1906: The dog died suddenly without having been ill so far as could be observed. Weight 8200 G.

Autopsy.—The skin and mucous membranes were very pale, the viscera were deeply colored, but apparently not congested. The heart appeared enlarged and distended with dark venous blood. A small amount of pericardial fluid was found. The lungs were collapsed and congested.

Histologic Examination.—The two kidneys appear the same except for the lesions made by the needle in the left kidney; its parenchyma and capsule show injury. In both kidneys the capsule, glomeruli and tubules are normal except in the immediate vicinity of the lesions just noted. The lumen of the tubules appears empty or containing a small amount of cell detritus. The heart, aorta, liver and lungs are normal.

SODIUM CHLORID.

Normal salt solution, 0.8 per cent., was used as a control to see what effect on the kidney the injection of an isotonic non-toxic solution would have.

PROTOCOL 9.

Dog.—Black and white female fox terrier. Weight 8180 G.; no albumin or casts in urine after four months of probation period; specific gravity 1020.

Between Jan. 11 and Feb. 27, 1906, nineteen injections of normal salt solution of 6 c.c. each were given into the left kidney.

March 24, 1906: In fine condition, no albumin.

Feb. 25, 1907: Weight 9800 G.; in fine condition, no albumin.

July 19, 1907: Killed by destroying the medulla by pithing. Weight 7940 G.; active and alert though thin.

Autopsy.—Left kidney showed an area of thickened capsule where it was adherent and contracted. Right kidney and the other organs are normal.

Histologic Examination.—The heart, aorta, liver, and right kidney present wholly normal structure. The left kidney shows much thickened capsule with areas of newly forming connective tissue in the cortex and as deep as the medullary portion, obliterating the tubules and resembling the wedges of productive connective tissue resulting from decapsulation of the normal kidney, or the kidney in chronic nephritis, with the exception that the areas in the kidney under consideration are long, narrow and confined within pretty distinct limits, suggesting strongly that these areas represent the scar tracts left by the penetrating needle.

MECHANICAL INJURY.

Two dogs were used to test the effect of the mechanical injury of inserting a hypodermic needle in the renal parenchyma.

PROTOCOL 10.

Dog.—White and brown female terrier, weight 6130 G.; at the end of a two-months' probation period. No albumin or casts.

Between Jan. 11 and 31, 1906, the hypodermic needle was passed into the left kidney nine times.

January 31: Being in doubt as to the accuracy of my manipulation of the needle, the dog was lightly chloroformed with the intention of locating the needle more exactly in the kidney. Unfortunately the dog died under the narcotic, but the needle was found to have been placed directly into the kidney.

Autopsy.—Nothing abnormal was found except a few recent hemorrhagic areas in and beneath the kidney capsule.

Histologic Examination.—No variations from normal were found except slender tracts of young connective tissue in the left kidney.

PROTOCOL 11.

Dog.—Yellow mongrel female. After three months of probation period, weight 6550 G.; no albumin or casts.

Between Feb. 1, and 27, 1906, the left kidney was needled twelve times.

Feb. 14, 1907: After a period of severe mange accompanied by diarrhea and loss of weight to 3600 G. the dog died.

Autopsy.—No macroscopic changes noted except total absence of fat throughout the body; kidneys showed no gross lesions.

Histologic Examinations.—The liver specimen was excessively hardened and could not be sectioned. The heart muscle and aorta appear normal. The lungs show congestion and in a few small areas, the alveoli are filled with blood though not presenting the appearances of inflammatory consolidation. The left kidney shows a thickened capsule with dense connective tissue pressing irregularly on the cortex and in places invading it. There is new connective tissue formation in several narrow areas deep in the parenchyma of the kidney, presumably the lines of needle puncture. Except for these evidences of injury there is no appearance of nephritis, the glomeruli and tubules appearing normal.

SUMMARY B.

1. Injections of alcohol into the kidney substance cause connective tissue increase in the kidney, resulting in an interference with the nour-

ishment of the tubules and the glomeruli, which resembles the milder grades of chronic productive nephritis.

2. Adrenalin injected into the kidney substance is not of itself the cause of any circulatory or inflammatory changes locally, although the injury incident to injection shows a resulting scar.

3. The use of the hypodermic needle without any injection fluid, and the use of normal saline injections into the kidney substance, are both followed by the formation of connective tissue tracts in the kidney which resembles the replacement fibrosis which occurs in chronic nephritis. That is, the structural changes observed in nephritis in man is imitated, but there is no general distribution of the connective tissue throughout the kidney such as appears when there is a true inflammatory process.

C. EFFECT ON THE KIDNEY OF INCREASED VISCOSITY OF THE BLOOD DUE TO THE ADDITION OF GELATIN TO THE BLOOD STREAM; AND OF SOLUTIONS OF ADRENALIN CHLORID AND OF ACETATE OF LEAD.

GELATIN.

In spite of the fact that increased viscosity as a possible cause of renal disease has been examined and found wanting by Hirsch and Beck,[7] it seemed possible that if gelatin were added to the blood over a period of days some circulatory or structural changes might be found in the kidney. Opitz[8] has found that gelatin solutions increase the viscosity of dog's blood promptly and to a considerable degree.

PROTOCOL 12.

Dog.—Black and white mongrel male, weight 10000 G. After three months' probation period; no albumin or casts in urine; specific gravity 1048.

Between Jan. 18 and Feb. 27, 1906, nineteen injections of 5 per cent. gelatin in water of 6 c.c. were given into one of the superficial veins of the dog's legs.

No albumin or casts were found at any time in the urine of this dog, and on July 19, 1907, he was killed by "pithing." In fine condition, weight 9320 G.

Autopsy and histologic examination revealed no variations from normal in any tissue.

ADRENALIN CHLORID.

The use of repeated doses of adrenalin chlorid in the general circulation causes temporary vasoconstriction in all the vessels of the body except those of the lungs, a great contraction of the kidney vessels and a temporary decrease in the secretion of urine. This is a matter of common laboratory observation and has been made the subject of exact record recently published by Schlayer and Hedinger.[9] Such a phenomenon,

7. Hirsch and Beck: Deutsch. Arch. f. klin. Med., 1902, lxii, 560.

8. Opitz: Arch. f. d. ges. Physiol., 1900, lxxxii, 447.

if repeated, might be expected to cause some permanent alteration in the blood supply, function or structure of the kidney.

PROTOCOL 13.

Dog.—Unfortunately the dog used for this test was infected after seventeen injections of 3 c.c. each of adrenalin chlorid solution, and death resulted from pyemia a few days later.

Histologic Examination.—The histologic picture of the kidneys was that of acute degeneration with hemorrhages in the parenchyma. No conclusions could be drawn from this test and time was lacking to repeat it.

ACETATE OF LEAD.

As a control test to have some recognized type of experimentally produced nephritis to compare with the lesions produced by the other procedures used in this study, the intermuscular injection of solutions of acetate of lead was adopted.

PROTOCOL 14.

Dog.—Feb. 22, 1906: White and black terrier, male, weight 9850 G. After three months' probation period the urine showed no albumin or casts. Over a period of two months injections of 1 c.c. each of a 10 per cent. solution of acetate of lead were given in the muscles of the legs.

August 14, 1906. For the past two weeks, convulsions and considerable loss of weight.

Autopsy.—Except for the smallness and hardness of the kidneys no variations from normal were found.

Histologic Examination.—The heart muscle shows no abnormal structure. The section of the aorta shows no thickness of the elastic coat, no separation of the elastic fibers and no infiltration or degeneration of the endothelial coat. The vasa vasorum appear healthy. The liver appears normal. The kidneys show no change in the capsule as to their thickness or vascular supply. The glomeruli are distended, everywhere filling the capsule of Bowman completely. The tufts appear to be the seat of active cell proliferation. The capsular cells are not increased. There is no atrophy, but a uniform swelling of the glomerular tufts. The tubular epithelium fills the lumina almost everywhere. There is little cellular detritus in the tubules. The cells lining the straight and convoluting tubules are swollen. There are occasional hemorrhages among the tubules, in some of which absorption is in process; others are evidently recent. The condition resembles that of a mild chronic degeneration more than a chronic productive nephritis which would probably result if the poisoning had been more severe or the period of observation longer.

SUMMARY C.

1. Increased viscosity of the blood due to the presence of gelatin does not affect the kidneys.

2. Lead acetate solution caused a chronic degeneration of the kidneys.

3. Although the test with adrenalin was inconclusive, this failure is not of vital importance, as Loeb[10] found that inflammatory processes

9. Schlayer and Hedinger: Deutsch. Arch. f. klin. Med., 1907, xc, 1.

10. Loeb: Am. Jour. Med. Sc., 1905, cxxx, 665.

never resulted from adrenalin injections, the effect being degeneration processes in various stages.

DISCUSSION.

The function of the healthy kidney depends on three main classes of factors. Of paramount importance is the blood flow through the kidney, which may vary in its pressure, its rate, and the size of the vascular path to and from the glomeruli and the convoluted tubules. The quality of the blood reaching the kidney is important, as it has been shown to affect renal secretion through variations in its chemical composition, its temperature, its viscosity, and its osmotic pressure. Direct and reflex nervous stimulation also has been shown to alter the activity of the renal epithelium.

When we find errors in the function of the kidney we must look to some alteration of the normal nerve control, or to some defect in the quality of the blood, or to some error in the character of the circulation. Even grave defects of function may exist and persist even for long periods, as, for example, the excessive diuresis in diabetes insipidus, without necessarily being accompanied by any appreciable alteration in the secreting cells or in the blood vessels of the kidney.

Very considerable alteration of the kidney structure is frequently found without any suspicion having been aroused of faulty function of the kidney, either by the general health of the individual before death, or by exact analysis of the urine. It is apparent, then, that the experimental study of chronic diseases of the kidney can not be expected to give a full answer to the question of etiology.

Histologic examination of kidneys often reveals advanced structural changes which have not been suspected by a faulty function during life.

Urinary analysis fails to supply an altogether reliable source of information as to changes of renal structure, and still less in regard to temporary errors in the function. Blood analysis, as by cryoscopy, supplements our other means of diagnosis, but is not invariably sufficient to point to the exact character or degree of renal disease.

Delafield[11] tersely states: "Any educated physician will now admit that albumin may be absent with kidney disease and present without it."

A recent test, applied by Schur and Weisel,[12] which, it is claimed, will detect the presence in the blood of nephritics of a substance exerting the mydriatic effect of adrenalin on the frog's eye, may add to our means

11. Delafield: Lectures on the Practice of Medicine, New York, Part I, S 17; Part IV, 412-496.

12. Schur and Weisel: Wien. klin. Wchnschr., 1907, xx, 699.

of diagnosis. They say that the sera of normal people do not give this reaction.

We may expect as much information from the accumulation of clinical data as from animal experimentation.

A summary of the procedures which have been adopted in animal experimentation shows only a few which have actually resulted in the approximation of lesions such as are found in chronic nephritis in man. Ophüls[13] considers that Ehrlich[14] and Levaditi[15] have produced chronic nephritis by the use of vinylamin. Paessler and Heineke[16] obtained chronic nephritis by operative removal of large parts of the kidney substance. Posner[17] quotes Orth as having obtained nephritis in rabbits by subcutaneous bruising of the kidney. Similar lesions have been produced in the present study by coagulation infarcts due to the injection of alcohol into the kidneys. These lesions, due to operative removal, chemical or mechanical injury, and subsequent fibrous repair, are all similar to the cases of chronic productive nephritis reported in the experimental results of Johnson,[18] Emerson, [19] and Osmoloffski[20] after decapsulation of the kidney in animals.

Among the means which have been used to cause the production of interstitial changes in the kidney are aloin, boracic acid, cantharidin,[21,9] potassium chlorate, chromic acid, potassium bichromate,[22] salts of lead,[13] mercury[9] and arsenic,[9] oxalic acid, oxamid, sulphuric acid, the toxins of the pneumococcus and of the diphtheria bacillus,[9] uranium nitrate, theocin,[20, 23] excessive amounts of chlorids[24] and phosphates,[25] alcohol[26] and nephrotoxic serum.[3]

Caro[27] found nephritis in cats from five to eight days after experimental removal of the thyroid.

Of all these procedures, the use of small doses of the salts of lead is

13. Ophüls: Jour. Am. Med. Assn., 1907, xlviii, 483.
14. Ehrlich: Internat. Beitr. z. inn. Med., 1902, i, 647.
15. Levaditi: Arch. internat. de pharmacod., 1901, viii, 45.
16. Paessler and Heineke: Verhandl. d. deutsch. path. Gesellsch., Berlin, 1905, p. 99.
17. Posner: München. med. Wchnschr., 1906, liii, 531.
18. Johnson, H. A.: Ann. Surg., Philadelphia, 1903, xxxvii, 592-601.
19. Emerson, H: Am. Jour. Med. Sc., 1904, p. 692.
20. Osmoloffski: Russk. Vrach, 1903, ii, 801.
21. Brodzki: Berl. klin. Wchnschr., 1906, xliii, 906.
22. Blank: Ztschr. f. klin. Med., Berlin, 1906, lx, 400.
23. Heineke and Myerstein: Deutsch. Arch. f. klin. Med., 1907, xc, 101.
24. Weber: Arch. f. exper. Path. u. Pharmakol., 1905-6, liv, 1.
25. Leopold: Ztschr. f. klin. Med., 1906, lx, 481.
26. Friedenwald: Jour. Am. Med. Assn., 1905, xlv, 780.
27. Caro: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1907, xvii, 447.

the only one which is known to produce regularly a chronic nephritis in man and animals. All the other procedures have resulted in degeneration of the kidney of an acute or chronic character, or have caused but temporary lesions which leave no permanent effect on the kidney parenchyma.

We have, then, two methods which caused what resemble the lesions, but not the clinical picture of chronic nephritis in man: the use of lead salts and the formation of scar tissue within or on the surface of the kidney. It is true that neither of these can be considered as frequent causes of nephritis in man.

The causes usually included in the etiology of chronic nephritis in man come under four headings:

1. Infectious diseases: scarlet fever, diphtheria, pneumonia, typhoid fever, tuberculosis of any part of the body, septicemia, and erysipelas.

2. The poisons of gout, rheumatism, syphilis, and lead.

3. Vices of appetite; the excessive use of nitrogenous and other stimulating foods and drinks.

4. Errors persistent, or frequently repeated, in the circulation; cardiac disease; exposure to wet and cold; muscular fatigue; attacks of acute or chronic congestion and degeneration of the kidney; attacks of acute exudative nephritis; mental worry and anxiety.

Loeb[28] would add that non-nephritic albuminuria leads in a high percentage of cases to a real nephritis, and his reasoning to this end is important. He finds that orthostatic albuminuria is, in a majority of cases, of cardiovascular origin. A diminished blood flow through the kidney with increased pressure in the renal vein is the cause of renal hyperemia. This condition is often due, according to Krehl,[29] to the "cor juvenum."

Again, J. Rose Bradford,[30] although denying that all cases of orthostatic albuminuria lead to a chronic lesion, explains the increase of albuminuria in a convalescent from acute nephritis when assuming the erect posture, by the less advantageous circulation which the kidney obtains in this position.

Delafield[11] gives cases to show that albuminuria appears after prolonged exertion owing to a congestion of the kidneys. After cessation of the exertion the albumin regularly disappears within a few hours.

28. Loeb: Deutsch. Arch. f. klin. Med., 1905, lxxxv, 348; lxxxiii, 452.

29. Krehl: Deutsch. med. Wchnschr., 1905, xxxi, 1872; Deutsch. Arch. f. klin. Med., 1906-7, lxxxviii, 351.

30. Bradford: Brit. Med. Jour., 1907, i, 725.

Fothergill[31] (1887) states that the knowledge of that time warranted the conclusion that "the waste-laden condition of the blood causes a contraction of the tiny arterioles producing high tension. The sustained high arterial tension sets up atheromatous changes in the arterial walls, and from this spring a number of maladies." While this idea has much to support it and has been widely accepted up to the present time, the studies of Slade,[32] of Sollmann[33] and of Opitz[8] suggest that this conception is wrong, and that in the case of meat extractives, although there is a general contraction of all smooth muscle tissue, a vasodilatation of the kidney vessels occurs.

Slade found that: (1) Muscle extracts increased the rate and activity of the heart. (2) Blood vessels are constricted. (3) Plain muscle of the whole body shows increased movement. (4) In the form of beef tea, moderate diuresis accompanied by vasodilatation of the kidney occurs.

Sollmann finds that if the viscidity of the blood is increased a dilatation of the renal arteries and veins occurs in the perfused excised kidney, and that blood has a dilator effect on the vessels of the excised kidney.

Opitz finds that a heavy meat diet materially increases the viscosity of the blood in dogs.

It would be easier to accommodate this series of experimental results in a theory which postulated a dilatation of the kidney vessels at a time when the other vessels of the body are contracted, rather than in any supposition which demands that the kidney must share uniformly in the contraction of the blood vessels of the body at large. When there is an increase in proteid extractives in the blood, the viscosity of the blood is increased, and if these substances remained in the body they would do harm. The stimulus of these harmful substances is apparently responded to by two circulatory changes, a constriction in the vessels of the body at large, causing high blood pressure, and a dilatation of the vessels of the kidney. These alterations in the circulatory distribution would at once put the kidney in the best possible condition to secrete, i. e., a wide capillary path and high general blood pressure, providing a maximum amount to pass through the kidney in a given time.

That there is a general vasoconstriction and general rise of blood pressure is a common observation in nephritis, but it can not at all be claimed that constriction of the renal vessel occurs coincidently, and it is

31. Fothergill: Vaso-renal Changes versus Bright's Disease, New York, Putnam, 1887.

32. Slade: Jour. Physiol., 1907, xxxv, 165.

33. Sollmann: Am. Jour. Physiol., 1905, xiii, 24.

to be noted particularly that the splanchnic blood vessels do not necessarily exhibit vasomotor changes identical with those of the skin and muscles. The effect of cold on the surface of the body is to contract the vessels of the skin, and this is usually accompanied by diuresis, as Dubois and Butruille[34] have recently demonstrated so successfully, and in this case the increased activity of the kidney must be supposed to be due to the presence of more blood in the kidney, which can not itself be directly affected by the cold which constricts the vessels of the surface of the body.

As Graupner[35] says, high blood pressure occurs in nephritis as soon as substances are retained that should be excreted, and it drops spontaneously as soon as the renal function is re-established. Or it may be said that an increase in the substances to be excreted puts more work on the normal kidney. Increased function demands increased blood flow. This is accomplished under physiologic conditions by a rise in blood pressure due to increased heart action and vasoconstriction, and we may suppose to a dilatation of the renal vessels, although a positive proof of this is not at hand.

Morse[36] thinks that a certain proportion of cases of chronic nephritis in man may be due to the action of chemical substances produced by bacteria, inasmuch as the human kidney is more or less constantly exposed to the action of such substances.

Grund[37] finds that cystoscopy, ureteral catheterization, and stone in the bladder cause reflex interference with renal functions to such a degree as to lead to grave errors in the functional powers of the kidney, as well as to difficulties in drawing reliable conclusions from urinary analysis under such conditions.

Carter,[38] in a critical and experimental study of the etiology of nephritis in Galveston, Texas, concludes that the excessive use of meats in a warm climate and carelessness in recognizing and treating infectious diseases, and not the climate *per se*, are responsible for the prevalence of kidney disease in that region.

v. Homeyer,[39] in a study of nephritis in the German army from 1884 to 1904, found the commonest cause of acute nephritis to be the infectious diseases scarlet fever, tuberculosis and diptheria. Second in fre-

34. Dubois and Butruille: Echo méd. du nord, 1907, xi, 253-255.
35. Graupner: Berl. klin. Wchnschr., 1907, xliv, 453.
36. Morse: Jour. Exper. Med., 1896, i, 613.
37. Grund: München. med. Wchnschr., 1906, lxii, 1803.
38. Carter: Med. News, New York, 1904, lxxxv, 919.
39. Homeyer: Ueber die Haufigkeit der Nierenkrankheiten in der deutschen Armee 1884-1904, Inaug. Diss., Munich, 1907.

quency as a cause of acute nephritis he found to be chilling and wetting of the body, as by sleeping on the damp ground. He found that chronic nephritis was often traceable to chilling, and excessive bodily exertion to the degree of fatigue, especially in men who had passed through an acute nephritis at an earlier date.

Delafield says,[11] "As soon as the blood accumulates in the veins to any considerable extent, the kidneys suffer. One of three things regularly happens to them: either a chronic congestion, chronic degeneration or chronic nephritis is developed." And, again: "The same mechanical obstructions to the circulation—heart disease, pleuritic effusions, etc.—which produce chronic congestion can, instead of this, produce chronic degeneration."

It must be apparent that Councilman's[40] conclusion is correct: that kidney disease is not an entity, but that the kidney is secondarily affected.

If we examine the causes of nephritis as they have been outlined in the four classes above, it will be noticed, I think, that there is one important factor either constituting the entire cause, as commonly accepted, or playing an important part, if not an usually accepted part, in each instance. I have reference to circulatory stagnation in the kidney. In the infectious diseases the exact physiologic effect of the several bacterial toxins has not been completely studied. We have enough clinical data, however, to supplement the few experimental results that are available.

The work of Paessler and Romberg[41] showed that the cause of death in diphtheria and in experimentally produced pneumonia was due, not to cardiac failure, but to a toxic paralysis of the peripheral or central vasomotor control, resulting in vascular stasis.

In typhoid fever[42] and tuberculosis[43, 44, 45] low blood pressure exists for long periods, and there is some experimental proof that the toxins of the tubercle bacillus, at least, have a marked vasodepressor action.

In streptococcus infections, as septicemia, erysipelas, and we might almost say in scarlet fever, the uncomplicated results on the circulation

40. Councilman: Jour. Am. Med. Assn., 1906, xlvi, 81.

41. Romberg and Paessler: Arch. f. exper. Path. u. Pharmakol., 1899, xlii, 283.

42. Janeway, T. C.: Am. Jour. Med. Sc., 1907, cxxxiii, 50.

43. Regnault: Le cœur chez les tuberculeux, Paris, 1899.

44. Arloing, Rhodet and Courmont: Cong. p. l'étude de la tuberculose, Paris, 1891, ii, 29.

45. Charrin and LeNoir: Compt. rend. Soc. de biol., Paris, 1893, v, series 9, p. 769.

are those of low blood pressure, the pressure not rising in scarlet fever until albuminuria is established.

In nephritis following gout, rheumatism, syphilis and chronic lead poisoning, the case is not so clear, but it must be kept in mind that in all four of these instances there is a marked tendency to fibrous tissue formation, especially in the walls of the blood vessels. The high blood pressure which results from chronic arteritis may be preceded by stages of insufficient pressure which we fail to recognize clinically.

Where we are considering what I have called vices of appetite or habit it will be noticed that the substances mentioned are all classed commonly as stimulants, in that they produce temporary increase in cerebral activity. Excess of activity is compensated for physiologically by relaxation and rest, and I believe that it is not too much to claim that in all instances where abundant use of meat and stimulants is indulged in the circulation undergoes considerable depression after the immediate effect of the increased activity has passed. The dilated facial capillaries of the hearty eater and drinker are an evidence of vascular stasis following frequently repeated over-stimulation.

What I believe can be shown to be the entire cause of chronic nephritis in many cases is the result of the various disturbances included in the last group. Exposure to wet and cold cause a central congestion by peripheral constriction in the skin and muscles. Muscular exertion, if carried to the degree of fatigue, results in general relaxation of vascular tone. Previous attacks of acute exudative, acute congestive and acute degenerative nephritis leave the kidney especially susceptible to subsequent congestion, and are, if repeated, sufficient cause for persistent congestion and nephritis. The pale surface and tightened artery of the man under the strain of business or professional cares is familiar, and every such picture presents an instance of physiologic fatigue, in which the vasomotor center is being excessively stimulated and the heart is pumping against unnecessarily high resistance. The result is visceral congestion.

Congestion causes functional inadequacy in any tissue. Inadequacy of renal function causes, among other things, according to Leopold,[24] a retention of chlorids and phosphates in the blood, and the presence of an excess of chlorids and phosphates in the blood may cause albuminuria, which of itself is a sign of faulty function and faulty circulation.

The improvement in chronic nephritis under such treatment as is directed chiefly to maintaining the circulation at a constant level of efficiency is an indication that circulatory error probably shared in the

causation of the disease. Webster's[46] summary of the treatment of chronic nephritis may properly be taken as a type of treatment that would be generally accepted. He advises dietetic moderation beyond the point of supplying ample food to carry on bodily functions and maintain nutrition; woolen clothing, bathing, open-air life where there are no rigors of climate; exercise never to the point of fatigue, to maintain the cardiovascular equilibrium at its most efficient point.

The suggestions with which Janeway[42] supplements Loeb's[27] theory of the causation of increased arterial tension and cardiac hypertrophy in chronic nephritis show a similar conviction to the one I have expressed.

"In chronic kidney disease we must look for some cause of the increased pressure. May it not be that the conditions of the circulation in the kidney are such that an increased pressure must be maintained in order to accomplish the necessary amount of secretion? Any local or general cause of slow blood flow, or low blood pressure, or congestion or stagnation in the renal circulation would at once be met by an increase in general blood pressure. If this is continually persisted in, it is entirely conceivable that it might become permanent. Increased arterial pressure is a symptom, or, more truly, a proof of the body's defensive action against disease."

Or as Loeb himself says: "Cardiac hypertrophy and increased blood pressure are compensatory reactions, occurring when the glomeruli are imperfectly supplied with blood, because inflammation or stasis has allowed too low a capillary pressure for proper filtration."

Schlayer and Hedinger[9] note that every injury to the renal vessels resulting in an error of circulation expresses itself in a diminution of diuresis.

CONCLUSIONS.

From experimental results it would appear that interference with the blood supply of the kidney can be accomplished by means of chemical injury to the renal parenchyma, and that the process of repair which ensues may involve such a destruction of secreting tissue as to cause the death of the animal.

From the experimental use of general vasodilators, it appears that the kidney suffers at least mild grades of degeneration, which may be due, not to the specific renal irritation of the drugs employed, but to the defective blood supply which frequently repeated vascular relaxation causes.

From an analysis of the accepted causes of chronic nephritis in man it is evident that many of them have as a common factor a more or less

46. Webster: Am. Jour. Med. Sc., 1907, cxxxiii, 271.

severe and prolonged stagnation in renal blood supply, and, although this factor is often accompanied by the presence of irritants which we recognize as injurious to the kidney tissue, insufficient blood supply alone will cause, first, an error in the function and later an alteration in the structure of the kidney.

As convincing proof of the true cause or causes of chronic nephritis in man is not present, we must perforce accept as a theory one which will account for most of the known facts. Loeb's explanation of the probable sequence of the circulatory events coincident with the course of chronic nephritis in man might reasonably be supplemented by an explanation of the etiology of nephritis which recognizes as a frequent, if not an invariable factor, deficient renal circulation. Faulty function always results from deficiencies of blood supply and if the defects persist or are frequently repeated faulty structure results. In the case of the kidney, the fault in its function resulting from the altered structure in chronic nephritis will cause much or little disturbance in the body at large according to the degree of circulatory compensation which can be maintained. Cardiac disease, bacterial toxins, and metabolic waste products are probably the causes of the errors in circulation which cause, first, faulty function in the kidney and, finally, chronic nephritis.

If this theory of etiology is supported by subsequent study, its application to the prevention of nephritis might strengthen existing efforts to check the spread of infectious disease, and to urge moderation in the habits of over-stimulation and over-work, which are prominent in present day life in large centers of population.[47]

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47. In addition to the above, the following references will be found of interest: Barr: Brit. Med. Jour., 1907, i, 725. Georgopulos: Ztschr. f. klin. Med., Berlin, 1906, lx, 411.. Josué: Presse méd., 1907, xv, 233. Lutheus: Arch. f. exper. Path. u. Pharmakol., 1906, lv, 116. Paessler: Samml. klin. Vortr., 1906, new series, No. 2, p. 408. Paessler and Rolly: Deutsch. Arch. f. klin. Med., 1903, xvi, 217. Riegel: Ztschr. f. klin. Med., Berlin, 1884, vii, 260. Thayer: Am. Jour. Med. Sc., 1904, lxxvii, 391.

THE PREVENTION OF TROPICAL ABSCESS OF THE LIVER BY THE EARLY DIAGNOSIS AND TREATMENT OF THE PRESUPPURATIVE STAGE OF AMEBIC HEPATITIS.*

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During the last seven years I have enjoyed most exceptional opportunities for studying tropical abscess of the liver in Calcutta, and have now arrived at the conclusion that the disease can and should be prevented altogether in the great majority of cases. The following are briefly the steps by which I have reached this position:

In 1902[1] I published a paper on tropical, or amebic, abscess of the liver and its relationship to amebic dysentery, in which I gave tables to show that I had found living amebas in scrapings from the walls of 35 out of 37 consecutive liver abscesses, the two negative results being in those not examined until twelve or more days after the abscess had been opened and drained. Further, two-thirds of the abscesses, when first opened, were sterile as regards the presence of bacteria. Kruse and Pasquale had previously found amebas in only 6 out of 15 cases examined. I also showed that when both a clinical history and a postmortem record were available, in over 90 per cent. of the cases dysentery was found to be associated with the liver abscess, and in 95 per cent. of these there was evidence that the dysentery had preceded the formation of the abscess, while it was always, in my experience, of the amebic variety. I, therefore, concluded that tne large tropical abscesses (as opposed to those due to suppuration in the portal veins or in the bile ducts) were always due to the *Amœba dysenterica,* and secondary to amebic dysentery, although the latter might often be of a latent nature, giving rise to no typical dysenteric symptoms during life, but revealing itself in the form of a few amebic ulcers found postmortem, usually high up the large bowel in the cecum or ascending colon.

In a second paper[2] in 1903 I gave an account of amebic dysentery in India and discussed the formation of amebic abscess of the liver. In 1905[3] I dealt with the value of leucocytosis in the early diagnosis of

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* Read at the fifth annual meeting of the American Society of Tropical Medicine, held at Baltimore, March 28, 1908.

1. Brit. Med. Jour., Sept. 20, 1902.
2. Brit. Med. Jour., June 6, 1903.
3. Brit. Med. Jour., 1905, ii, 1291.

amebic abscess and pointed out that, although occasionally an attack of acute hepatitis with leucocytosis may clear up without suppuration occurring, yet, if such cases are followed up, sooner or later an abscess of the liver nearly always forms. I also narrated a case of acute hepatitis with leucocytosis, which cleared up under large doses of ipecacuanha.

In 1906[4] I published two cases of amebic abscess of the liver successfully treated by aspiration and injection of the soluble bi-hydrochlorid of quinin, without drainage, having found that the amebas in thick liver abscess pus could readily be killed by that drug in a strength of from 1 in 100 to 1 in 500, a method which has since proved effective in other hands, especially in early deep-seated abscesses, although it fails in many more advanced cases.

While on the lookout for the early stages of the disease for this line of treatment, I met a number of cases of fever with leucocytosis and symptoms of acute hepatitis, in some of which aspiration failed to reveal any abscess. They yielded, however, very rapidly to full doses of ipecac, thus showing that the increase of the leucocytes takes place before actual suppuration has taken place and sometimes many days earlier. Last year (1907) I published[5] a series of such cases which were rapidly cut short in the presuppurative stage by the ipecac treatment, which may be briefly summarized as follows: Fifteen cases were met in the Calcutta European General Hospital during twelve months. In only three was there a clear history of dysentery or symptoms of it while in the hospital, and they lost their fever and hepatitis after two to four days' ipecac treatment, although they had previously suffered from fever for 15, 34 and 41 days, respectively, and one had been aspirated for liver abscess with a negative result. In three more cases of acute hepatitis without dysentery not treated by ipecac, the fever subsided only after 34 to 49 days. In five similar cases treated with ipecac the fever subsided in 1 to 6 days, although it had previously persisted for 13 to 50 days, one patient having been aspirated for liver abscess with a negative result. Lastly, there were three cases of fever with no signs of either dysentery or hepatitis, other than very slight painless enlargement of the liver, but with leucocytosis of the same type as in the other cases, namely, without very marked increase of the polynuclears (usually from 70 to 80 per cent.). They had suffered from fever for 35, 45 and 53 days, respectively, but it ceased in two to fifteen days under ipecac treatment. This is the class of case in which a large, deeply-seated, fibrous-walled

4. Brit. Med. Jour., June 16, 1906, i.

5. Practitioner, Lond., 1907, lxxviii, 776; Tropical Fevers in the Tropics (Oxford Medical Publications).

abscess of the liver forms very insidiously with irregular intermittent fever, commonly treated as malarial, but with no very obvious signs of hepatitis until a very late stage. Two of the above fifteen cases relapsed and returned to the hospital 4 and 7 months later, respectively, each with an amebic abscess of the liver.

When dysentery is present and complicated by hepatitis, ipecac is advised by Sir Patrick Manson and other authorities, but at the time the above paper was published I was unable to find any recent writer who recommended large doses of ipecac for hepatitis when not accompanied by dysentery, although several of the older Indian authors, especially McClean and Norman Chevers, strongly urged its use in such cases also. The considerations which led me regularly to adopt this treatment were:

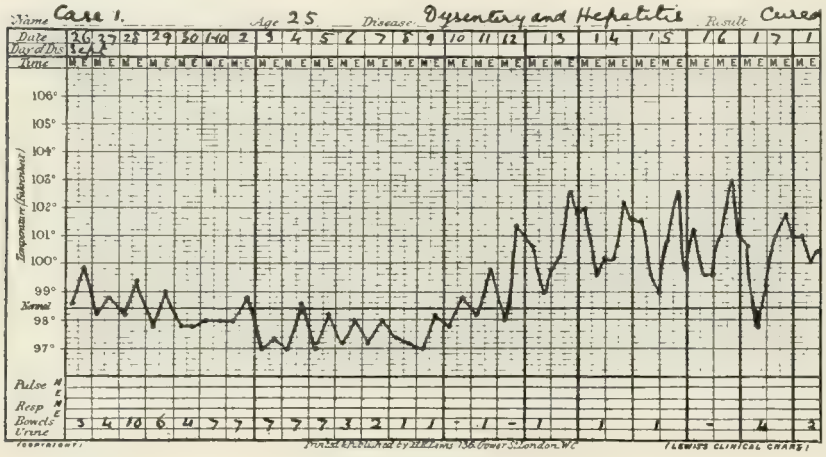

Chart 1—Case 1.

First, finding dysentery associated with 90 per cent. of tropical abscesses of the liver, and, second, the fact above mentioned that in many patients dying of liver abscess, without history or symptoms of dysentery, amebic ulcers are found postmortem in the upper part of the large bowel. I, therefore, regarded hepatitis accompanied by leucocytosis as an indication of the presence of latent amebic ulceration of the large bowel, which indicated large doses of ipecac for its cure. The results of this treatment, both those mentioned above and subsequent ones, have been so successful that during the last two years no instance of liver abscess developing while the patient was in the European General Hospital, Calcutta, has occurred, although a few patients have been admitted with an abscess

already formed. On the other hand, a number of very acute hepatitis cases have cleared up under ipecac after an abscess had been suspected, and in five instances also sought for in vain with an aspirating needle.

REPORTS OF CASES.

The following three examples, which have occurred within the last two months, will serve to illustrate the value of this method of early diagnosis and treatment:

VERY ACUTE HEPATITIS CLOSELY FOLLOWING ON DYSENTERY RAPIDLY CURED BY IPECAC.

CASE I.—A European, male, aged 25, was admitted for dysentery of six weeks' duration, passing about six stools daily containing blood and mucus, without pain or straining. He was treated with a castor oil mixture and creolin

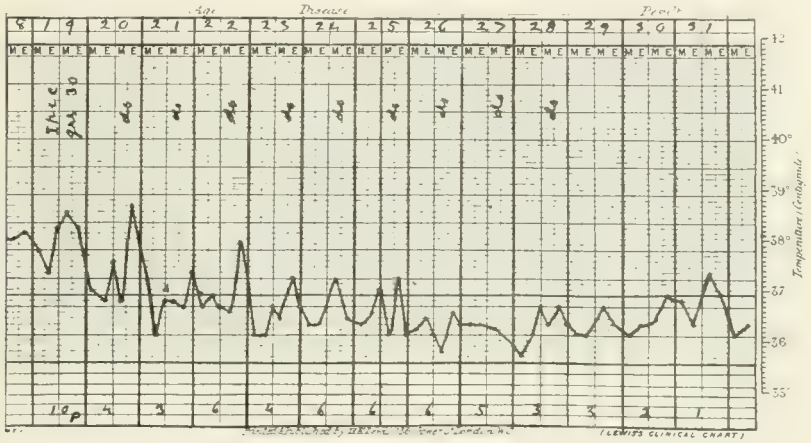

Chart 1 Case 1.—Continued.

enemas, and the blood and mucus disappeared from the stools after ten days. Seven days later (September 11) he began to have pain in the hepatic region and in the right shoulder, and his temperature, which had previously been slightly subnormal, began to rise (Chart 1). The liver dulness was not increased, extending from the sixth rib to the costal margin. The pain continued to be severe, and on the 13th the breath sounds were noted to be weak at the base of the right lung. Morphia was being given for the pain, and ten grains of quinin three times a day for the fever. On the 15th there was profuse sweating, while the liver dulness now extended up to the fifth rib. Five leeches applied over the liver relieved the pain somewhat. On the 16th the right lower chest was observed to be moving less than the left, and on the 18th *x*-rays showed that the diaphragm on the right side was quite motionless, while there appeared to be a slight shadow in the right lobe of the liver. Abscess of the liver was, therefore, diagnosed. As, however, there had been recent dysentery, which had not been treated with full doses of ipecac, the physician in charge of the patient (who had over twenty years' Indian experience) agreed to use the ipecac treat-

ment for a short time before operating on the liver abscess, the existence of which he did not doubt. Thirty grains of the drug were given daily from the 19th to the 27th, with the result that the temperature steadily fell, as shown in Chart 1, and the signs of acute hepatitis simultaneously subsided. On the 20th the pain over the liver and the sweating had both diminished and he slept better. By the 21st the pain had ceased over the liver, although it continued in a slight degree in the right shoulder for another day. On the 23d the temperature was normal and there was no pain or sweating, and all suspicion of liver abscess had disappeared. The patient was kept in the hospital up to the 22d of November, but had no more signs of dysentery or hepatitis and gained weight steadily. There was no shadow of doubt in the minds of all who watched this patient that the ipecac treatment averted suppuration in the liver.

DYSENTERY FOLLOWED BY HEPATITIS WITH TEMPORARY IMPROVEMENT. VERY ACUTE HEPATITIS TWO AND ONE-HALF MONTHS LATER SUCCESSFULLY TREATED WITH IPECAC.

CASE 2.—European, male, aged 26, admitted Aug. 20, 1907, with a history of dysentery eight months before, followed after three weeks by pain in the epigas-

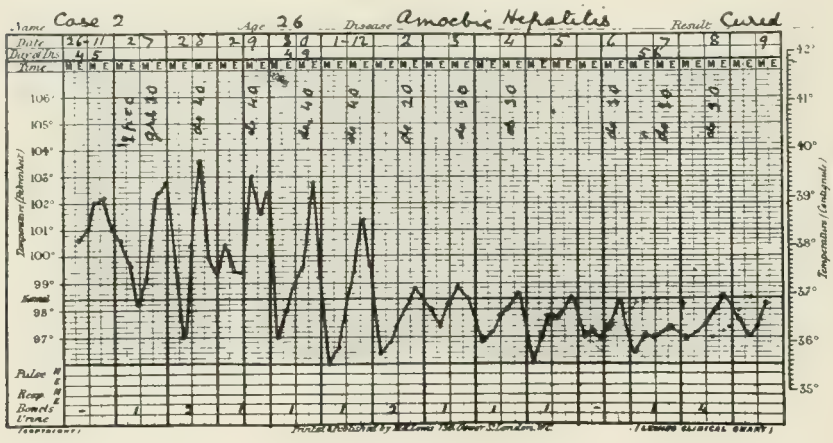

Chart 2—Case 2.

trium. On admission he had slight enlargement of the liver with pain over it. Stools loose, but no blood or mucus; intermittent fever rising to 101 or 102 F. in the evenings. The diaphragm moved well, and there was only slight increase of the leucocytes, with but 65 per cent. of polynuclears. The symptoms of hepatitis subsided in three weeks under salines and quinin, and he left the hospital apparently well. He returned two and a half months later (November 26), having had fever every evening for the previous month and a half, with rigor at times and sharp pain over the liver on and off. His bowels had been constipated. He was now weak and thin. There was slight bulging, without marked tenderness, in the hepatic region. The breath sounds at the right base were diminished, with a decrease of vocal fremitus and vocal resonance. The liver dulness extended from the fifth space to three inches below the costal margin in the nipple line. No edema was present, and the spleen was not enlarged. Under *x*-rays the right half of the diaphragm was found to be two inches higher than the left and scarcely moved even with deep respiration, but there was no shadow. A blood

count showed 3,570,000 red corpuscles, 15,000 white; ratio of white to red, 1 to 236; polynuclears, 77 per cent.; lymphocytes, 13 per cent.; large mononuclears, 9 per cent., and eosinophiles, 1 per cent. On account of the acuteness of the symptoms and the fulness in the hepatic region, liver abscess was suspected, but it was determined to try the ipecac treatment before operating, so 30 grains were given on the evening of the 27th and 40 grains on the following four evenings. On the 28th and 29th the hepatic pain was distinctly less, and the patient could turn over on his right side, which he could not do before. On the 30th there was no pain or tenderness over the liver. On December 2 his temperature remained normal for the first time, and a steady convalescence ensued, the liver receding until it was only just felt beneath the costal margin. The ipecac was continued in 30-grain doses at increasing intervals up to Jan. 5, 1908, in order to guard against the possibility of a relapse, and he left the hospital apparently quite well on January 5. The rapid lessening of the pain, followed by the decline of the fever and enlargement of the liver under the ipecac, was most striking in this case, and indicated that this treatment saved the patient from suppuration in the liver.

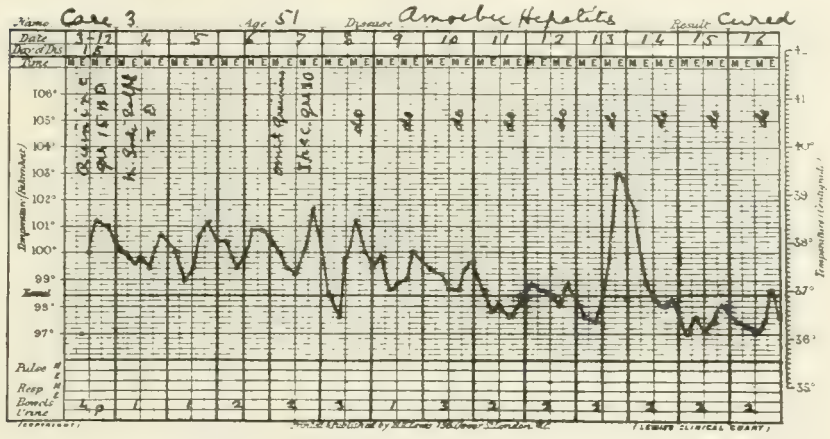

Chart 3. Case 3.

HEPATITIS WITHOUT HISTORY OR SYMPTOMS OF DYSENTERY RAPIDLY SUBSIDING UNDER THE IPECAC TREATMENT.

CASE 3.—European, male, aged 51, admitted on Dec. 3, 1907, for fever. He had been ill for two weeks with fever and pain in the right hyphochondrium, with nausea and loss of appetite. No rigors, but feels chilly at times and sweats at night. Bowels constipated. The liver extends one inch below the costal margin and was very tender. Other organs normal. A blood count on the 11th showed 4,670,000 red corpuscles, 12,875 white; ratio of white to red, 1 to 363; polynuclears, 81 per cent.; lymphocytes, 12 per cent.; large mononuclears, 6, and eosinophiles, 1 per cent. Ipecacuanha was commenced on December 7, 30 grains being given each evening. Two days later the temperature began to fall and reached normal on the 11th, after which there was only one rise on the 13th, accompanied by a rigor, being possibly malarial in origin. On the 17th the liver had become reduced in size, being only just felt below the ribs, and the patient left the hospital apparently quite well on December 22 (Chart 3). This is an example of the less acute form of hepatitis, which drifts insidiously on into

suppuration after weeks of intermittent fever. It is only one step further to the class already mentioned, in which there is no pain or tenderness over the liver, and the presence of leucocytosis alone raises a suspicion of the true nature of the case, which is confirmed by the chronic fever yielding rapidly to large doses of ipecac.

METHODS OF GIVING IPECAC.

In giving large doses of ipecac in amebic dysentery and hepatitis, precautions have to be taken to avoid vomiting, especially if it is possible that an abscess of the liver has already formed. The usual method is to give either tincture of opium or chloral hydrate some twenty minutes before the freshly made pills or bolus of ipecac, no food or drink being given for several hours before and after the dose, which is best administered once a day in the evening. Recently I have had the drug put up in quantities of five grains in keratinised capsules, which are not dissolved until they reach the small intestines. This has worked very well, no antecedent sedative being required. Dr. F. B. Grubbs, of the United States Army, has recently informed me that the same desirable effect is obtained by coating ipecac pills with melted salol, but I have not yet had an opportunity of trying it. From 30 to 60 grain doses of the drug have been used, but the smaller quantity appears to be efficient. It should be continued for at least two weeks at increasing intervals, as two of my earlier cases, in which the ipecac was discontinued as soon as the temperature fell, relapsed some months later, presumably owing to the latent amebic ulcers not having been completely cured.

DURATION OF THE PRESUPPURATIVE STAGE OF AMEBIC HEPATITIS.

There remains to be considered a very important question: What is the usual duration of the presuppurative stage of amebic hepatitis, during which the ipecac treatment will avert the formation of an abscess of the liver? An examination of my records of the last seven years has furnished the following data on this point: Out of 53 native patients admitted to the hospital with liver abscess, often bulging through the thoracic or abdominal wall, 51 per cent. gave a history of over two months' illness, and 38 per cent. more between one and two months; 9 per cent. from two weeks to a month, and only one case, or 2 per cent., had been suffering for less than two weeks. Among 26 cases in Europeans there had been fever of hepatitis for over one month in 50 per cent., for from two weeks to a month in 34.6 per cent., and of less than two weeks in only 15.4 per cent, the times being 9, 9, 11 and 13 days, respectively, in these four cases. It is clear from these figures that in the vast majority of instances there is ample time for the diagnosis by blood examinations, etc., and for the ipecac treatment being carried out

during the presuppurative stage of acute amebic hepatitis. Very rarely multiple abscesses may develop within a few days with extreme acuteness, but even here the only chance of saving the patient is in the immediate ipecac treatment.

My experience of this treatment leads me to believe that it is not too much to say that over 90 per cent. of amebic abscesses of the liver can and ought to be prevented by the methods described in this and in previous communications, and thus one of the greatest scourges of some tropical countries may be conquered by the prompt use of a simple medicinal treatment, based on the correct conception of the true pathology of the disease derived from prolonged combined microscopic and clinical observation.

SNAKE POISONING IN THE UNITED STATES:

A STUDY BASED ON AN ANALYSIS OF 740 CASES.

PRENTISS WILLSON, M.D.
WASHINGTON, D. C.

General introduction.

PART 1.—The poisonous snakes of the United States.

Classification, number, distribution, habits and identification of the various species.

Anatomy and physiology of the poison apparatus.

PART 2.—Snakebite in the United States; frequency, pathology, symptoms, complications and sequelæ, duration, cause of death, diagnosis, prognosis and treatment.

General summary and conclusion.

Knowledge concerning snake poisoning in the United States is decidedly meager. The infrequency of the occurrence and the mildness of the symptoms in so many of the cases, do not encompass the subject with a degree of practical importance sufficient to stimulate much interest in it; hence the articles in the text-books are incomplete, in some instances contain serious misstatements, and uniformly convey to the casual reader totally erroneous impressions. The obviously important subject of the geographical distribution of the different venomous species has been practically ignored. The mortality and prognosis have remained largely matters of conjecture. Small effort has been made to bring the recommendations for treatment up abreast of the recent advances in our knowledge of the toxic properties of venoms. For these reasons the present paper has been undertaken. I have aimed at making the consideration a practical one, but have not hesitated to draw fully on the voluminous literature of the experimental side of the subject.

PART 1.—THE POISONOUS SNAKES OF THE UNITED STATES.

In the animal kingdom, one of the orders under the class *Reptilia,* is *Ophidia,* which includes all the true snakes. The *Ophidia* are divided into two sub-orders, *Ophidia colubridæ* and *Ophidia viperidæ,* or colubrine and viperine snakes respectively. The colubrine snakes are largely absolutely harmless, although the venomous species belonging in this sub-order are among the most deadly known. Fortunately the list of colubrine species in the United States includes only two which are sufficiently venomous to be dangerous to man. These are the coral snakes which will be described in detail later. The viperine snakes are divided

into two families, the *Viperinæ,* or true vipers, and the *Crotalinæ,* or pit-vipers, all the species in both families being venomous. The true vipers are confined entirely to the old world. The pit vipers are more universal in their distribution, but the greater number is found in the Western Hemisphere. With the exception of the two venomous colubrine species, the coral snakes, all the poisonous snakes found in the United States belong to this family.

THE CROTALINE SNAKES OR PIT VIPERS.

The pit vipers have been so named because of the presence of a pit or fossa on the side of the face below and between the nostril and the eye. The various species found in the United States belonging to this family represent three genera, *Crotalus, Sistrurus* and *Ancistrodon.* Of these the first two are all rattlesnakes· while the last is represented by but two species, the copperhead, *Ancistrodon contortrix,* and the water moccasin, *Ancistrodon piscivorus.*

Thirteen species of rattlesnakes, and three or four varieties sometimes placed as distinct species, are found within the limits of the United States. Formidable as this statement appears it is in reality far from being so, as will be seen when the distribution of these species is studied. These snakes, so named from the termination of the tail in the rattle, a structure too well known to require description, are placed in two genera, the distinction being made because of a different arrangement of the scales and plates covering the dorsal surface of the head.

Sistrurus.—In the genus *Sistrurus* the integument covering the head is arranged in a series of large plates, in a manner similar to that found in the harmless snakes and in all the venomous species save rattlesnakes of the genus *Crotalus.* The two distinct species included in the genus are the ground rattler, or pigmy rattlesnake, *Sistrurus miliarius* and the massagua, *Sistrurus catenatus.* The little ground rattler rarely exceeds eighteen inches in length. It is found only in the South, from North Carolina, along the Gulf into Texas, and for some distance up the southern tributaries of the Mississippi. The massagua is larger than the preceding species, adult specimens measuring between two and three feet. It ranges from well into Canada through western New York, Michigan, Ohio, Indiana, Wisconsin, Minnesota, Iowa, Illinois, Nebraska and Kansas, being rare and in places exterminated in many parts of the range mentioned. In Texas and the Southwest it is replaced by a variety of the typical species, *S. catenatus Edwardsii.*

Crotalus.—The species of rattlesnakes belonging to the genus *Crotalus* are eleven in number in the United States. All of these are char-

acterized by having the head covered dorsally with scales quite like those found on other portions of the body, the large plates being fewer in number and differing in arrangement from those in the genus *Sistrurus*. The distinction between these two genera of rattlesnakes has a practical interest for the physician, the two species belonging to *Sistrurus* being much less dangerous than those of *Crotalus*. Of the eleven species of the latter genus, only a few need be mentioned specifically. The diamond-back rattler, *Crotalus adamanteus,* the largest of our venomous species, attains a length of over eight feet. It is distributed through Georgia, Florida and the Gulf States to the Mississippi. In Texas it is replaced by a slightly smaller species, *C. atrox*. In the North, this genus is represented by three species: In the East, extending from New England to Florida and westward to Texas, Iowa and Kansas is found the banded or timber rattlesnake, *C. horridus*. This specie aver-

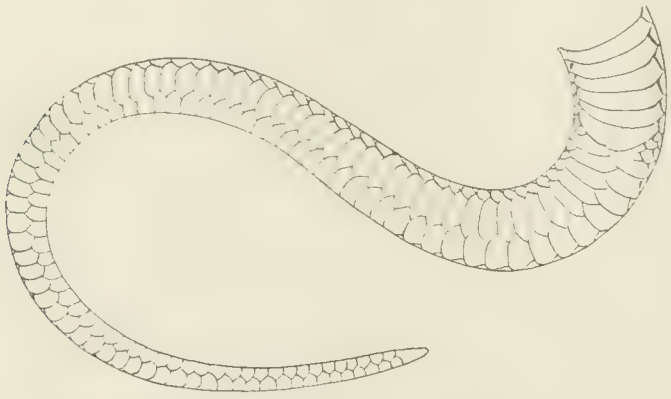

Fig. 1.—Underside of tail of water snake, *natrix* (after Stejneger).

ages from three to four feet in length for adult specimens, and rarely, if ever, exceeds six feet in length. In the states of the Middle West, from Canada to Texas, the prairie rattlesnake, *C. confluentus,* is found. Its average length is a little over three feet. West of the Rocky Mountains, from British Columbia to Southern California, the Pacific rattlesnake, *C. oregonus (C. lucifer),* is the only rattlesnake found. The six species of the genus *Crotalus* which have not been specifically mentioned are confined to the territory extending from the Mississippi through Texas, Arizona, Nevada, New Mexico, Utah and Southern California. Of these several are very rare and extend only a slight distance north of the Mexican boundary.

Ancistrodon.—The copperhead and the southern water moccasin are the only two species representing the genus *Ancistrodon* in the United

States. The copperhead, *A. contortrix,* is also known in different portions of its range as the red adder, chunkhead snake, pilot snake, upland moccasin, spreadhead snake, or moccasin. It is essentially an eastern species, extending as far west as Kansas, Oklahoma and Texas. Its northern limit is probably central Massachusetts, although it has been described from Vermont. In the South it is common, except in the peninsular portion of Florida, where it seems to be entirely absent. Michigan, Wisconsin, Nebraska and probably Iowa are free from this reptile. This is not a large species, adult specimens seldom, if ever, exceeding three feet in length, most specimens being considerably shorter. It frequents rocky hillsides bordering water courses, sometimes fields and woods, and is particularly likely to conceal itself under loose planking and rocks around barns and other out buildings. The general color is brown. Dorsally, the ground color is a bright hazel brown, which is very bright and distinct on the head. On either side of the body there are from fifteen to twenty-six dark chestnut colored irregu-

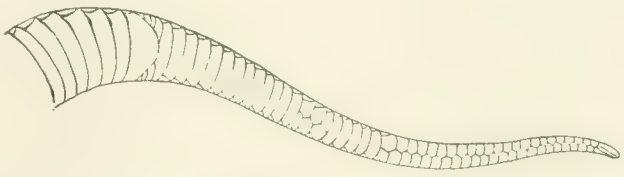

Fig. 2. Underside of tail of water moccasin (after Stejneger).

larly triangular blotches, the base of the triangles resting on the ventral scales, the apices being in the median line dorsally. Ventrally the general color is a dull yellow, irregularly marked with dark blotches.

A snake frequently mistaken for the copperhead is the hog-nosed snake, *Heterodon platyrhinus.* This absolutely harmless species is mentioned here because, as stated, it is so often confused with the copperhead, and because even when properly identified it is almost always stated to be venomous. The dread in which it is popularly held is shown by the common names given it, such as sand viper, spreading adder and blowing adder. This snake is readily distinguished from the copperhead by the absence of those features to be described later, which render the recognition of the venomous species so easy, and in addition, by its turned-up snout, different coloring, and characteristic habits. Being fond of basking in open sandy spots, where rapid escape is impossible, the hog-nosed snake has evolved for its protection the ingenious habit of making itself look even more terrifying than the really dangerous species. In the presence of danger, it flattens

the head, expands the anterior portion of the body, and blowing and hissing strikes right and left at the object of its dread. If handled roughly it sometimes bites, but as I know from experience the wounds inflicted are merely a few tiny superficial abrasions with absolutely no after effect.

The water moccasin, *Ancistrodon piscivorus,* sometimes called the cotton-mouth or branch moccasin, is a southern species. It is fairly common in different localities in North Carolina and becomes more frequent in the states farther south, being most common in all the Gulf states as far as the Mexican boundary. It ascends the Mississippi into Missouri, southern Illinois, and western Kentucky, and is reported up

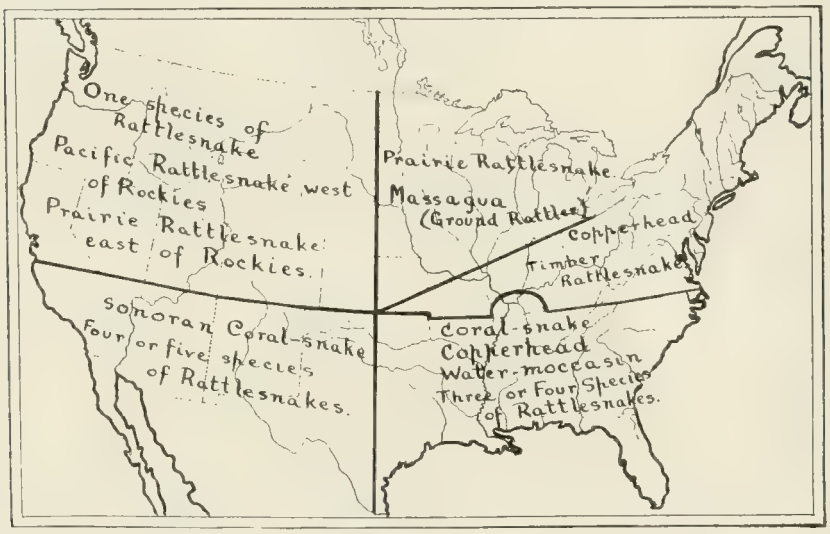

Fig. 3.—Distribution of the Poisonous Snakes in the United States.

the Ohio river as far as the Wabash. By way of the Arkansas river it invades the state of the same name, probably extending into Oklahoma. In eastern Texas it ascends the rivers as far as Dallas, and is very common in all that part of the state bordering on the Gulf. The water moccasin is semiaquatic in its habits and is seldom found far from water. It prefers to bask in the hot sun, stretched out on half submerged rocks and logs, and also climbs into the branches of the low bushes overhanging water. The rice fields of Louisiana fulfill all the conditions required by this species, and in them it is very common and greatly feared by the negro laborers. This snake is larger in every way than the copperhead, and some specimens exceed four feet in length. Its

general color is a very dark blackish brown, frequently so obscured by the dried mud clinging to it as to be scarcely recognizable. Its head is a dark purplish black in color and the body is marked on either side by from twenty to thirty narrow bars of the same color. Ventrally the animal is black, mottled with blotches of a dirty white.

The evil reputation of this reptile has spread far beyond the area infested by it, and as a result all water snakes are held in ill repute. As a matter of fact the reverse is the case, the water moccasin being the only venomous species showing any fondness for the water. Several water snakes are confused with the dangerous species, as is shown by the popular names bestowed upon them, such as copper-bellied moccasin and banded water moccasin. These are all varieties of the harmless water snake, *Tropidonotus fasciatus.* A large southern species, occurring coincidently with *A. piscivorus,* is *Tropidonotus toxipilotus;* although a dangerous looking reptile it is perfectly innocuous. All these harmless species may be differentiated from the true water moccasin, by the difference in color and the absence of the characteristic features of the pit vipers to be detailed later. In addition it may be stated that *T. fasciatus* and its varieties are distributed over a wide area in which the venomous species is never found.

THE VENOMOUS COLUBRINE SPECIES.

Of all the colubrine snakes in the United States, the two species sufficiently venomous to be dangerous to man are the coral snake or harlequin snake, *Elaps fulvius,* and the Sonoran coral snake, *Elaps euryxanthus.* These two species are so closely related and so similar in every way as to make their distinction of no practical importance to the physician. Both are confined in their distribution to the southern states. The range of *Elaps fulvius* is similar to that given for the water moccasin. It is found from North Carolina throughout the Gulf states to western Texas and ascends the Mississippi as far as southern Ohio. *Elaps euryxanthus* is a western species the range of which has not yet been definitely settled. It is known to be confined to the states of the Southwest and seems to be most numerous in Arizona. These two very interesting and very dangerous reptiles are fortunately rarely encountered by man. They are retiring in disposition, and spend most of their time burrowing under ground or hidden under the bark of old logs or in the dead leaves. The body is slender, rarely over three feet in length, and the head is small and only slightly differentiated from the neck. The color pattern is a most striking one, consisting of alternate broad rings of red and black, completely encircling the body, and

separated by narrow rings of yellow. On the tail the red rings disappear, the color being alternately black and yellow.

The general appearance of the coral snakes is more or less closely simulated by several harmless species, particularly by the different varieties of the milk snake, *Ophibolus doliatus*. The distinction may be made by remembering the distribution and habits of the coral snakes, and also that in them the colored rings extend across the ventral surface of the body, while in the harmless species the abdomen is white or blotched, and shows no trace of the rings. In the venomous species the black rings are bordered with yellow, the reverse being true in non-venomous snakes.

An interesting group of colubrine snakes, the *Opistoglyphs,* is of much more importance to the herpetologist than to the physician. They are mentioned here for the sake of completeness, and because they contribute toward swelling the total number of venomous species, stated by text-books to be found in the United States. The *Opistoglyphs* are characterized by the possession in the posterior portion of the upper jaw of a series of grooved fangs, intended for the injection of venom. These structures place them undeniably among the poisonous colubrines, but the position of the fangs in the back of the mouth, and the small size of the species found in the United States renders it very doubtful if the bite of these reptiles would be more than the most trivial affair. So far as as I know, not a single case of bite by any of these species has been reported. Brief notes on the species found in the United States are appended: The Jews-harp snake, *Trimorphodon lyrophanes,* and the annulated snake, *Sibon septentrionalis,* reach a length of from two to three feet. Both are confined to the states of the extreme southwest and are the only species which may be considered as possibly capable of inflicting poisoned wounds in man. The black banded snake, *Erythrolamprus imperialis,* found in southern Texas, attains a length of about one foot. Four species of *Tantilla,* one in the southeast and three in the southwest are absolutely innocuous for man, being hardly larger than large earth worms.

THE IDENTIFICATION OF THE POISONOUS SNAKES.

An ability to differentiate correctly between the harmless and venomous snakes may frequently be of the greatest importance. In the preceding descriptions of the various venomous species, mention has been made of the harmless snakes most likely to be confused with them. Here it is intended to point out those general features possessed by all the poisonous snakes, which fortunately are sufficiently characteristic

Fig. 4.—Lateral view of Skull of *Crotalus horridus* (from a photograph). 1. Active fangs. 2. Reserve fangs. 3. Upper maxillary. 4. Fossa for lodgment of the pit. 5. Lachrymal. 6. Frontal. 7. External pterygoid. 8. Quadrate. 9. Internal pterygoid. 10. Lower jaw.

to make their identification comparatively easy. The great structural differences between the viperine and colubrine species, make it necessary to consider the two separately.

All the pit vipers, rattlesnakes, copperhead, and water moccasin, correspond very closely with the popular ideas concerning the general appearance of the poisonous snakes. The head is broad and triangular and sharply differentiated from the neck. The body is thick and heavy in comparison with its length, and the tail short and blunt. The general sinister appearance of these reptiles is of little or no practical significance, however, since it is very closely simulated by many of the absolutely harmless species. The three features characteristic of all the pit vipers and of no other American species, the detection of any one of which establishes beyond all doubt the venomous nature of any given snake, are first, the presence in the anterior portion of the upper jaw of two hollow erectile fangs; second, the pit; and third, the presence on the ventral surface of the tail of scales undivided in the median line.

The fangs, as a very essential part of the poison apparatus, will receive detailed consideration later. It should be mentioned here, however, that in dead specimens they will be found folded against the roof of the mouth, very much as the blade of a pocket knife folds against the handle, and in this position are so covered by folds of the mucous membrane as readily to escape detection. By scraping the upper jaw from behind forward with some sharp object they may be brought into view. In addition to the fangs there is on either side of the upper jaw a single row of fine retrocurved teeth, while in the harmless species there is a double row on either side, the fangs being, of course, absent.

The pit, the structure from which the whole family receives its name, is a deep depression, lined by an epithelial membrane, which is lodged in a fossa on the outer aspect of the superior maxillary. It is seen in Figures 5, 17, and the fossa in the maxillary bone in Figure 4, 4. The rich supply of nerve fibers to the epithelial lining of the pit, renders it probable that the function of this peculiar structure is to act as an accessory sense organ. Although its exact function in the snake's economy is unknown, there can be no doubt that it serves as a most useful and unfailing means of recognizing the members of this dangerous family, and its absence in any specimen under examination, obtained in the United States, establishes its harmless nature, with the single exception of the coral snakes.

In Figures 1 and 2 is well illustrated a striking difference between the pit vipers and all the colubrine snakes, both harmless and venomous. In all snakes the ventral surface of the body as far back as the vent is

covered by overlapping scales, extending undividedly from one side of the body to the other. In the pit vipers many of these scales on the ventral surface of the tail, from the vent to the tip, retain this arrangement, extending unbrokenly across the body, while in the harmless species and also in the coral snakes, from the vent to the tip of the tail all the scales are divided in the median line. It is obvious, however, that it is not necessary to examine for this important point if the species of pit viper happens to be a rattlesnake. Here the presence of the rattle settles the venomous nature of the reptile at once.

In addition to the three important differential points which have been given consideration it may be mentioned that the pit vipers are ovo-viviparous, retaining the egg until the escape of the embryo. Some harmless species reproduce in the same way. The number of young produced by the pit vipers at one birth is comparatively small, many wild stories to the contrary notwithstanding. In the crotaline snakes, also, the pupil of the eye is vertical and cat-like, instead of round as in the colubrines. (Fig. 6, 19).

In identifying the coral snakes, the main dependence must be placed on the presence of the fangs, and on their peculiar and gaudy coloring, which has been described. In these reptiles the absence of the pit and the presence of divided scales on the ventral surface of the tail makes their positive recognition more difficult. The fangs of the coral snakes, as in the pit vipers, are situated in the anterior portion of the upper jaw, but differ from them in their comparatively and absolutely smaller size, and in being permanently erect. These differences will be explained more in detail later on. On either side of the upper jaw these snakes have but one row of teeth, the harmless species, as has been stated, having two.

GENERAL DISTRIBUTION OF VENOMOUS SNAKES IN THE UNITED STATES.

In Figure 3, the attempt has been made to indicate the number of venomous species in different portions of the country, rather than the exact limits of the range of the various species, which point has been given consideration above. It will be seen that in the greater portion of the North, one, and at most two species of rattlesnakes are all that are found in one locality, and that the only other venomous species present here is the copperhead, confined entirely to the East. In the South, the eastern states and Texas harbor three or four species of rattlesnakes, also the copperhead, water moccasin and coral snake; the western states having only the Sonoran coral snake in addition to several species of rattlers.

The reader is now in a position to pass judgment on the statement found in several text-books, that twenty-seven species of poisonous snakes are found in the United States. This figure, probably arrived at by counting up the number of species described by Stejneger,[1] includes seven species of opistoglyphs of no importance to the physician, and three species of rattlesnakes considered by many to be mere varieties. Eliminating these, the number remains at seventeen. To so state without proper qualifications, however, is to give impressions only a little less erroneous than those given by the larger number. Stejneger's work was written from the view point of the scientific herpetologist. From the point of view of the physician, it may be stated that the venomous snakes of the United States are the rattlesnakes, several species being described, the copperhead, the water moccasin and the coral snake.

ANATOMY AND PHYSIOLOGY OF THE POISON APPARATUS.

While an exhaustive account of the anatomy and physiology of the mechanism by means of which the poisonous snakes elaborate and inject their venom would obviously be out of place in this paper, a certain amount of knowledge on this subject is necessary to a comprehension of many points of practical importance in the consideration of snake poisoning. Such readers as may have a special interest in the subject are referred to Mitchell's[2] original account, or that given by Stejneger.[1] The poison apparatus will first be described as it exists in the pit vipers and then the differences existing in these structures in the coral snakes will be pointed out.

In Figure 4, a lateral view of a skull of *Crotalus horridus* is presented. It will be seen that the upper maxillary bone is greatly shortened from before backward. Externally it presents the fossa for the lodgment of the epithelial pit, and posteriorly articulates with the elongated external pterygoid. Above it articulates by means of a ginglymus joint with the lachrymal bone, which in turn articulates with the frontal. Below it bears the single perforated poison fang, firmly fixed in its socket and not in itself movable, as is often stated. Behind the active fangs are seen the reserve fangs, ready to be pushed forward to replace the active fang in case of its loss by accident or shedding. In the recent state these reserve fangs are completely hidden and surrounded by the mucous membrane. The fang itself is a hollow, curved tooth, the convexity of the curve being directed forward, containing two

1. Stejneger, L.: The Poisonous Snakes of the United States. Rep. U. S. Nat. Mus., 1893, Washington, 1895, pp. 337-487.

2. Mitchell, S. W.: Researches on the Venom of the Rattlesnake. Smithsonian Contrib. to Knowl., 1860, xii.

canals, an anterior and a posterior; of these the former is the canal for the venom, the latter the dental canal. The canal for the poison runs along the anterior convex border of the fang, from an upper aperture near the base of the tooth anteriorly, to the lower slit-like opening on the convex border near the point. The poison canal is lined by the same enamel as that covering the surface of the fang, showing the method of its formation, namely, an infolding of the anterior surface of the tooth. As has been stated, the normal position of the fang in the quiescent condition of the snake is folded back against the roof of the mouth, as is shown in Figures 5 and 6. In this position absolutely useless as a weapon, the fang is brought into a position of erection suitable for its use, by muscular action on the bony mechanism described. The muscle concerned is the sphenopterygoid, unfortunately not shown in any of the illustrations, which takes its origin from the median basal ridge of the skull, anteriorly, and passes backward and outward to be inserted into the inner aspect of the quadrate bone, seen at Figure 4, 8. It will readily be seen that the result of the contraction of this muscle will be to draw the quadrate forward, which motion will be imparted to the external pterygoid causing it in turn to act on the superior maxillary. As a result of the force so applied, and in virtue of its articulation with the lachrymal, the superior maxillary rotates downward and forward causing the fang to sweep through the segment of a circle until it comes into a position almost at right angles to the line of the upper jaw and most favorable for its use as a weapon of defense. In Figure 4 the fangs are shown in a position of almost complete erection.

The poison gland is an almond-shaped body lying below and behind the eye, extending backward to a point about on a line with the commissure of the lips. Its size varies with the size of the snake; a gland from a rattlesnake four feet long measuring eight-tenths of an inch in length (Mitchell). The gland is held in position by prolongations of its outer facial covering, the most important being the internal or suspensory ligament and the posterior ligament, running backward to the articulation of the lower jaw. Running through the center of the gland is a single slightly dilated duct, which receives the contents of the smaller ducts from the secreting acini. In this central duct and its prolongation from the gland to the base of the fang the venom is stored ready for use. The course of the duct is forward from the gland to the maxillary bone around which it winds to terminate in a manner to be described close to the upper aperture of the poison canal in the fang. Immediately under the eye, it presents a sharp curve and at the same point a noticeable enlargement due to the presence there of a band of muscular tissue

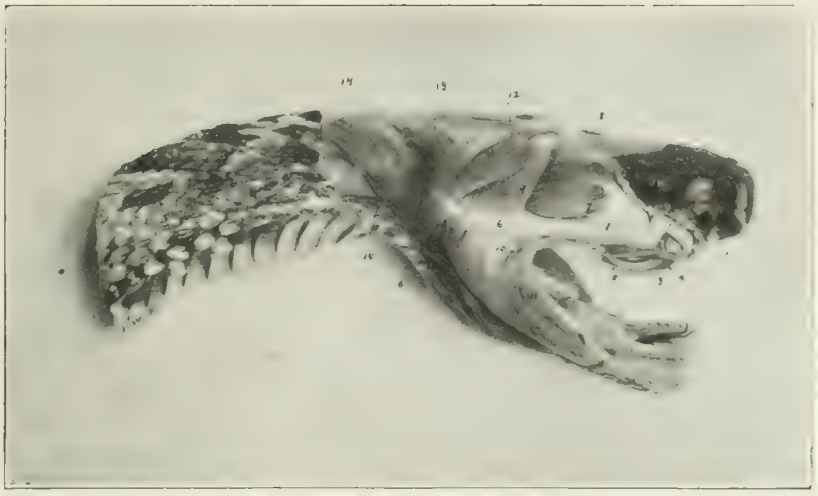

Fig. 5.—Superficial dissection of the poison apparatus of *Crotalus adamanteus* (from a photograph). 1. Poison gland. 2. Poison duct. 3. Fang. 4. Inner fang sheath. 5. Cut edges of outer fang sheath. 6. Posterior ligament of gland. 7. Anterior temporal muscle. 8. Middle temporal. 9. Posterior temporal. 10. Facial insertion of fibers of the middle temporal. 11. Mandibular portions of the anterior and posterior temporals. 12. Digastric. 13. Cervico-angular. 14. Cervico-mandibular. 15. Costo-mandibular. 16. External pterygoid. 17. Pit.

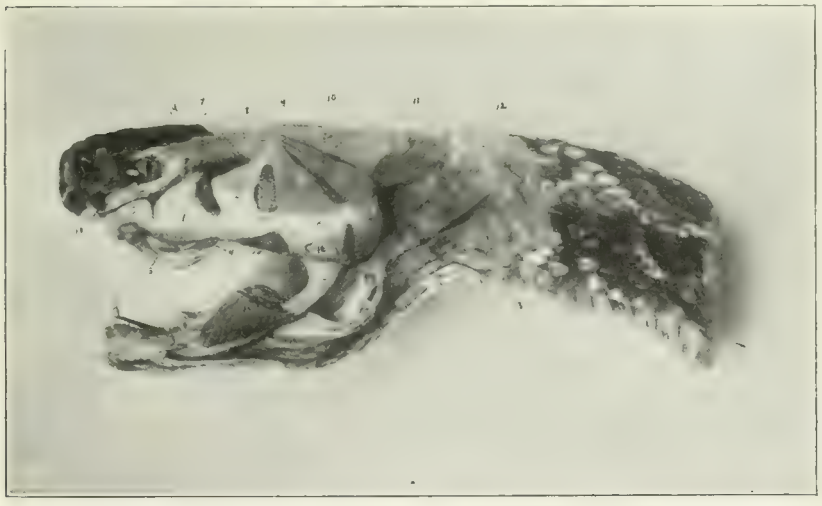

Fig. 6.—Deeper dissection of the poison apparatus of *Crotalus adamanteus* (from a photograph). 1. Poison gland. 2. Duct. 3. Fang. 4. Sheath of opposite fang. 5. Internal or suspensory ligament of gland. 6. Posterior ligament of gland. 7. Cut edges of anterior temporal muscle, showing the sharp down curving around the posterior border of the gland. 8. Middle temporal. 9. Posterior temporal. 10. Digastric. 11. Cervico-angular. 12. Cervico-mandibular. 13. Costo-mandibular. 14. External pterygoid. 15. Mandibular portion of anterior and posterior temporals. 17. Lower jaw. 18. Pit. 19. Vertical pupil.

constituting a true sphincter, first described by Mitchell.[2] The capacity of the duct from its cecal extremity in the gland to the sphincter varies, of course, with the size of the snake. Usually its capacity is but a few drops, and only in very large specimens does it exceed fifteen or twenty drops.

The relation of the poison gland to the two muscles now to be described is of the utmost importance. The anterior temporal muscle in the pit vipers has completely lost its attachment to the temporal fossa and takes origin entirely from the fascia covering the gland on its upper surface. From this origin the muscular fibers pass at first backward and then downward around the posterior border of the gland, passing between the suspensory and posterior ligaments of the same, and continuing downward find their attachment on the lower jaw. It will be readily seen that the contraction of this muscle will, in addition to closing the lower jaw, forcibly compress the upper and posterior portions of the gland. The external pterygoid muscle takes its origin from the posterior aspect of the articulation of the lower jaw. From this point it passes downward for a short distance and then turning sharply forward passes under the articulation internal to the ramus of the jaw and external to the quadrate bone and runs forward to a point directly under the poison gland, with which it is in the closest relation. The fibers of this muscle have the following three insertions: a portion, becoming aponeurotic, spreads out on and blends with the facial covering of the gland below and anteriorly. Another portion, becoming tendinous, is inserted into a tubercle on the posterior aspect of the upper maxillary bone just below its articulation with the external pterygoid. The third portion is lost in the sheath of mucous membrane investing the fang. When contracting, then, this muscle depresses the fangs by drawing the superior maxillary bone directly backward, thus proving itself the direct antagonist of the sphenopterygoid, which, as has been stated, causes its erection; presses on the lower and anterior portions of the poison gland; and finally, has an action on the sheath of the fang, yet to be described. It will thus be seen that the anterior temporal and external pterygoid muscles acting together subject the whole of the poison gland to a very considerable degree of pressure, calculated, if associated with the relaxation of the sphincter of the duct, to completely milk the gland and duct of their contents.

There now remains to be described the arrangement by means of which the venom expelled from the duct finds its way into the poison canal of the fang. As the fang lies in its quiescent condition against the roof of the mouth it is completely hidden from view by a tubular

sheath of mucous membrane. In Figure 5, this sheath is seen split open, its cut edges showing at 5 and the fang at 3. Toward the base of the fang this sheath seems to present an inner gum-like process, seen at 4, of firmer consistency than the rest of the sheath, closely clasping the fang just below the upper aperture of the poison canal. Into the cup-like cavity formed by the inner sheath, or gum, the opening of the duct from the gland is found. It will be seen, therefore, that there is no direct communication between the duct and the poison canal, the venom escaping from the former into the cavity of the gum-like structure around the base of the fang, and from thence taking the course along the path of least resistance through the only opening presenting itself, the upper aperture of the poison canal. When the fang is erected its membranous sheath becomes crowded back around the base, probably aiding by its pressure, in more closely approximating its inner portion to the base of the fang. Judging from the considerable number of muscular fibers passing into this sheath from the external pterygoid muscle, as has been described, there is reason to think that this approximation is decidedly an active, as well as a passive process.

In making use of the diabolically ingenious mechanism which has been described, the pit vipers have first to imbed the fangs in their victims and then to eject their supply of venom. In accomplishing the first of these objects, the reptile prefers to strike from a coil, although capable of inflicting its dangerous wounds from a great variety of positions. When angered or alarmed, the body is rapidly thrown into a series of circular coils, with the neck and upper portion of the body held loosely across the coiled mass in a succession of S-shaped curves. In the rattlesnakes the tail is held vertically, vibrating with wonderful rapidity, causing the well-known sound of the rattle. In launching itself forward to the attack the snake simply straightens out the S-shaped curves by contracting the muscles on their convexities. By this simple maneuver the head is shot forward with a speed which the eye can not follow. At the same time that the head is thrown forward, it is bent backward, the jaws opened to a surprising degree, and the fangs erected. The whole action is entirely comparable to a swift forward thrust with a double pointed dagger. Having thus imbedded its fangs the animal now proceeds with the injection of the venom; the various muscular acts described in this connection of course occur synchronously. With the fangs still imbedded in the tissues, they are drawn back and depressed, in order to deepen the wound, the lower jaw is forcibly closed on the part in a vicious bite, and the sphincter guarding the duct is relaxed. In performing these movements the anterior temporal and external pterygoid muscles are

brought into play, their contraction automatically compresses the whole of the gland and causes an ejection of venom from each fang into the tissues in which they are imbedded. Having accomplished its purpose the reptile disentangles itself from the wound and rapidly renews its coiled attitude prepared for further hostilities.

The essentials of the poison apparatus in the coral snakes are very similar to those in the pit vipers. On either side of the head there is a gland for the secretion of venom, connecting by means of a duct with a perforated fang, situated in the anterior[3] portion of the upper jaw. The fangs, however, are not depressible at the will of the snake, but maintain a permanently erect position, comparable to the canine teeth of the carnivora. They are both absolutely and relatively smaller than the fangs of the pit vipers of similar size. The mouth in these snakes is very small. For these reasons it is practically impossible for the coral snakes to inflict a wound except on the bare skin, and under exceptionally favorable conditions. In most of the few reported cases of bites of these species, the reptile has bitten while being carelessly handled. The action is a bite, pure and simple, the fangs being introduced with a chewing motion, and there is none of the striking seen in the pit vipers.

PART 2.—SNAKE-POISONING IN THE UNITED STATES.

The series of cases on which, in as large a measure as possible, this study is based, numbers 740 cases, of which 440 have been collected from the literature, and the remainder from various private sources. In both classes of cases, however, the clinical records have been so deficient, so lacking in the most essential details, that it has been found necessary to draw largely on the reports of the different investigators now working on venom intoxication along experimental lines. The section dealing with the toxicology of venom is intended only as a brief review of those phases of the present knowledge of this most interesting subject which have a direct and practical bearing on the matter under discussion. In regard to the frequency of occurrence of various symptoms and complications it has been considered inadvisable, and indeed impossible in most instances, to give exact figures, the number of full case reports being entirely too small to render such an attempt satisfactory. The figures given in the sections on mortality and prognosis, however, are based on a much larger number of cases than has before been available, and for reasons there presented are thought to be of considerable accuracy.

3. Noguchi's statement that the fangs in these species are situated in the posterior portion of the jaw, Osler's Modern Medicine, vol. i, page 248, is an error. See Stejneger, loc cit, page 356.

FREQUENCY.

The frequency of snake bite in the United States is largely problematical. In the older and more thickly settled portions of the country it is a rare occurrence. During the summer of 1907, however, two cases, due to the copperhead, occurred in the immediate vicinity of Washington, D. C. There can be no doubt that the poisonous snakes, especially the rattlesnakes, are being slowly but surely exterminated and as a result their bites are becoming more and more infrequent. Even in the South and Southwest, where the venomous species are most common, bites seem to be matters of rather rare occurrence. Many physicians practicing in these localities see but one or two cases in years of practice. Many cases, however, especially those due to the smaller rattlers and the copperhead, are never seen by physicians, the laity being well aware of the uniformly good prognosis of such cases. It is interesting to note that not a single case of snake bite is reported in the Medical and Surgical History of the War of the Rebellion, and that the condition does not seem to figure at all in the vital statistics of any of the states[4]. Everything considered my opinion would be that the total number of cases occurring annually is probably less than five hundred, possibly considerably less.

In regard to the relative frequency of bites by the different species more definite statements can be made. In 566 cases in the series in which the species of snake causing the injury was known, there were 408 cases of rattlesnake bite, 97 cases of copperhead bite, 53 cases of water moccasin bite and 8 cases of coral snake bite, representing respectively 72 per cent., 17.1 per cent., 9.3 per cent. and 1.4 per cent. of the series. The predominance of rattlesnake cases is only natural when the number of species and wide distribution of these snakes is considered. On the other hand, the figure of 17.1 per cent. for copperhead cases is probably too low. This snake is widely distributed in the eastern portion of the country and in many localities is the only venomous snake found. Its bite, however, is usually not a serious affair, and comparatively few cases receive medical attention. The habits of the water moccasin and its limited distribution accounts for the infrequency of bites by this species. As might be expected from the retiring habits of the coral snakes and the very small size of the mouth, bites by these snakes can only occur under most exceptional circumstances, as when the reptile is being carelessly handled, and the rate of 1.4 per cent. is entirely too high.

4. With the exception of Florida: the vital statistics for the years 1892 to 1899 give snake bite as the cause of death in thirteen cases.

PHYSICAL, CHEMICAL AND TOXIC PROPERTIES OF VENOM.

Venom is a viscid, greenish or yellowish fluid, usually clear, of acid reaction, and with a specific gravity ranging between 1035 and 1065. When dried it assumes the scaly, cracked appearance of dried egg albumen, and in this form retains its toxic properties almost indefinitely. In the process of drying there is a loss of from 25 per cent. to 50 per cent. in weight. Chemically, our knowledge of venom is far from perfect, and the exact classification of the various proteid constituents is still largely undecided. For the present purpose, however, any exhaustive discussion of this phase of the subject is unnecessary. It need only be said that, as first pointed out by two Americans, Mitchell and Reichert,[5] venom is a toxin of wonderfully complex activity, a complexity depending on the presence of a varying number of different toxic principles. Since the epoch-making experiments of these authors, serpent venoms have been investigated in laboratories all over the world, and the literature of the subject has reached voluminous proportions. The result of all this study has been to show conclusively that in venom we have one of the most complex poisons known. Those particularly interested are referred to the recent summaries of the subject, in French, by Calmette,[6] and in English by Martin and Lamb.[7] According to the latter of these authorities the following toxic principles have been found in the different venoms studied:

1. A powerful fibrin ferment.
2. An anti-fibrin ferment.
3. A proteolytic ferment.
4. Various cytolysins, capable of acting on red blood cells, leucocytes, endothelial cells of blood vessels, nerve cells and the cells of various other tissues.
5. Agglutinins for red blood cells, etc.
6. An antibactericidal body of the nature of anticomplement.
7. A neurotoxin or neurotoxins with affinities for all nerve cells, and especially the cells of the respiratory center in the bulb.
8. A neurotoxin, with an affinity for nerve endings in muscles and for those in the diaphragm in particular.
9. A substance which causes greatly increased tone in cardiac

5. Mitchell and Reichert: Researches on the Venoms of Poisonous Serpents, Smithson. Contrib. to Knowl., 1886, xxvi.

6. Calmette, A.: Les venins et les animaux venimeux, Paris, Masson et Cie, 1907.

7. Martin and Lamb: Snake-poison and Snake-bite, in Allbutt's System of Medicine, 1907, vol. ii, part ii, 783-821.

muscle, and if in sufficient concentration, systolic standstill of the isolated heart.

Venoms obtained from different species vary in the relative proportion in which these various toxic elements are present and apparently, also, in their absolute toxicity, and on these factors depend the variations seen in the syndrome of poisoning by the different species. In a general way, venoms group themselves in two classes, the venoms in either class being characterized by a more or less similarity in their physiological action, corresponding, respectively, to their origin from the two great divisions of the venomous snakes, the *Colubridæ* and the *Viperidæ*.

The geographical limitation of the subject renders it unnecessary to devote much space to a detailed consideration of the colubrine venoms. As has been stated, the only venomous colubrine species of practical importance in the United States are the coral snakes. Fortunately, bites from these reptiles are excessively rare, but the symptoms noted in the few reported cases show conclusively that their venom is similar in its action to the general action of other colubrine venoms, and accordingly dangerous. These venoms are characterized by the severity of their attack on the central nervous system, by their peculiar selective action on the respiratory center, and by the comparatively mild local manifestations at the site of their innoculation. In some venoms of this class a curare-like action on motor nerve endings, particularly those of the phrenics in the diaphragm, has been observed. I know of no experimental investigation of the venoms of the coral snakes except a few isolated experiments reported by Mitchell and Reichert.[5] On the other hand a knowledge of the action of the viperine venoms is of the greatest importance to the American physician, since at least 99 per cent. of snake bites in the United States are caused by the pit vipers. A careful study of the venoms of the rattlesnakes, copperhead and water moccasin is therefore necessary. Practically all the work done on rattlesnake venom has been with venom obtained from *C. adamanteus* and *C. horridus*. These two species are in a large measure typical of the other and smaller species of the same genus, and of the species of the genus *Sistrurus*. It has been demonstrated clinically, as will be shown later, that the bites of the smaller rattlesnakes are less dangerous than bites of the large species mentioned, but this is probably due to a decreased dosage, rather than to material differences in the toxic composition of the venoms. In general, the action of all viperine venoms as compared with colubrine venoms is characterized by the severity of the local symptoms at the site of innoculation, by a much less vigorous attack on

the central nervous system, and a greatly diminished tendency toward a selective action on the respiratory center. Many venoms of the true vipers, and practically all pit viper venoms, also show a pronounced tendency toward the production of hemorrhages in various parts of the body.

The comparative toxicity of water moccasin, copperhead and rattlesnake venom for guinea-pigs has been found by Flexner and Noguchi[8] to be in the order named. Thus taking 0.1 mg. of cobra venom as the amount necessary to cause the death of a pig weighing 300 gms. in less than four hours, these authors found that it would require twice as much water moccasin venom, six times as much copperhead venom, and ten times as much rattlesnake venom, to cause the same results under similar conditions. Although it has been shown that the toxicity of different venoms varies for different species of animals, it seems reasonable to suppose that if the minimum lethal dose of water moccasin venom for guinea-pigs is one-fifth that of rattlesnake venom, the former must be more toxic for man than the latter. It must be emphasized in this connection, however, that the relative degree of toxicity of these venoms, even if it could be proven to hold true for man, is an entirely different matter from the relative degree of danger attending bites inflicted by these snakes. In determining the latter point, as will be shown later, the relative toxicity of the venoms is only one of several points which must be given careful consideration.

The greater toxicity of the *Ancistrodon* venoms is due to the presence in them of greater amounts of the neurotoxic principle, as first pointed out by Mitchell and Reichert[5] and confirmed by Flexner and Noguchi.[8] These experimental findings receive some confirmation from clinical observations to be given later, and in beginning the consideration of the neurotoxic action of the pit viper venoms it must be stated that the moccasin and copperhead venoms in their action approach more nearly the type of colubrine poisoning than does rattlesnake venom. The latter, however, does contain neurotoxin, as has been conclusively shown by Flexner and Noguchi,[8] who so treated rattlesnake venom as to destroy all its toxic properties save those for the nervous system, and then found that they were able to cause the death of experimental animals by injecting the altered venom in doses of from ten to twenty times the minimum lethal dose of the unaltered venom. In these cases the symptoms observed were entirely like those following the injection of typical colubrine venoms. These experiments would seem to show

8. Flexner and Noguchi: Univ. Penn. Med. Bull., 1901-02, xiv, 438, and 1903-04, xvi, 163.

conclusively that the neurotoxins play a comparatively unimportant part in causing death in cases of rattlesnake poisoning, provided, of course, that we consider the relative toxic powers of the neurotoxins of rattlesnake venom to be approximately the same for man and the animals used experimentally, rabbits and guinea-pigs. For in order to cause death by the neurotoxic action of this unaltered venom it would have to be injected in doses which would be overwhelmingly poisonous from the large amount of various other toxic principles present. There can be little doubt, however, that the depression of the functions of the cord following the injection of pit viper venoms, plays a not unimportant part in causing the general collapse characterizing these intoxications. This depressive action seems to have a tendency to affect the sensory side before the motor, and may be marked by complete loss of function resulting in more or less anesthesia and loss of motion. The respiratory center shares in the general depression, but is not selectively attacked by rattlesnake and only to a slight degree by moccasin and copperhead venoms. Any selective activity of the neurotoxins of these venoms seems to be directed against the vasomotor center.

On the circulation all the pit viper venoms have a most decided action, causing a profound fall in blood pressure which is often, undoubtedly, the cause of death. This action, clearly demonstrated by the experiments of Mitchell and Reichert[5] for both *Crotalus* and *Ancistrodon* venoms, has been recently studied by Rogers[9] with the venoms of the rattlesnake and several old world vipers. The findings of this author I considered of the greatest importance. He observed, following injections of rattlesnake venom, a decided fall in blood pressure, associated with dilation and congestion of the entire portal system and resulting in a complete failure of the circulation. To this condition of the circulation he attributed the failure of respiration, considering this to be a purely secondary phenomenon in cases of viperine poisoning. The circulatory failure is attributed to the depression of the vasomotor center in the medulla, a conclusion entertained many years previously by Mitchell and Reichert.[5] The therapeutic procedures recommended by Rogers in view of his experimental findings, will be considered later. It will thus be seen that one of the most important actions of the pit viper venoms is to profoundly lower blood pressure, in fatal cases to such a point that respiration fails because of lack of circulation in the already impaired respiratory center.

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9. Rogers, L.: The Physiological Action and Antidotes of Colubrine and Viperine Snake Venoms, Phil. Tr. Royal Soc., London, 1901-1905, cxcvii, B., 123.

On the blood the venoms under consideration have several actions of the greatest importance; in producing or inhibiting coagulation, in causing hemolysis and agglutination, and in diminishing or destroying the bactericidal power of the blood serum.

The effect on coagulation is seen in both a positive and negative phase. Noguchi[10] is authority for the statement that the venom of *C. adamanteus* has the power to cause an immediate intravascular thrombosis, resulting in the speedy death of the subject. This intravascular thrombosis is rarely if ever the cause of death in actual cases of snake poisoning by American species, for in order to have this effect the venom would have to be received in large quantity immediately into the circulation, a combination of circumstances so excessively rare, as to be negligible. On the other hand, the negative phase, in which the clotting power of the blood is destroyed or seriously interfered with for a considerable length of time, is frequently observed clinically. It is doubtful, however, if this condition of the blood is of grave import, save in that it must predispose to the occurrence of hemorrhage.

The hemolytic and agglutinative properties of pit viper venoms are of greater theoretical than practical importance, and probably play a negligible part in actual cases of venom intoxication. Cytolysins and agglutinins for both red cells and leucocytes have been shown to be present in these venoms by Flexner and Noguchi.[8] Clinically the hemolytic action is shown by the frequent occurrence of hemoglobinuria. The relative power of these venoms to cause such blood changes is of interest as showing the difference in their toxic composition. Thus in causing hemolysis moccasin venom is fifty and copperhead venom twenty-five times as potent as rattlesnake venom, while in causing agglutination both moccasin and copperhead venom are twenty times as potent.

The great clinical importance of the changes induced in the bactericidal power of the blood serum by venom intoxication has not been sufficiently emphasized in the literature. Welch and Ewing[11] showed that in poisoned rabbits the blood serum had lost practically all its bactericidal properties, and to this condition they attributed the great rapidity of postmortem putrefaction. Flexner and Noguchi confirmed these findings with venoms of the rattlesnake, moccasin and copperhead. The relative potency of the venoms named in causing these changes does not seem to have been determined.

10. Noguchi, H.: Snake Venoms, in Osler's Modern Medicine, i, 247-265.

11. Welch and Ewing: The Action of Rattlesnake Venom on the Bactericidal Power of the Blood Serum, Med. Rec., 1894, xlv, 663; also Lancet, 1894, i, 1236.

TABLE 1. FINDINGS IN FOUR AUTOPSIES FOLLOWING DEATH FROM RATTLESNAKE BITES

Reporter.	Blood.	Brain and Cord.	Heart and Lungs.	Abdominal Viscera.	Local Findings.	Remarks.
1. Home[12]	Clots in heart.	Congestion of brain and its membranes, slight serous exudate.	Clots in heart. Half ounce of frothy fluid in pericardium. Lungs healthy.	Stomach congested, other viscera healthy.	Necrosis and sloughing of skin of arm. Finger had been amputated. Skin dissected up by offensive purulent serum. Some extravasation of blood in arm and on chest.	Death due to sepsis. Duration of illness 17 days.
2. Pihorel[13]	Fluid in cerebral sinuses and dura, coagulated in bitten arm.	Thickening of cerebral arachnoid and some adherence to dura.	Congestion of trachea and bronchi, which contained red, frothy mucus. Lungs healthy and crepitant, somewhat congested.	Healthy.	Very slight swelling around one bite. No changes in muscles.	Death after 9½ hrs. Surprisingly slight local manifestations.
3. Horner[14]	Entirely fluid, no coagulation	Consistence of brain normal, but deep brown color due to congestion. No extravasation of blood. Cord normal. Membranes of both cord and brain injected. Serous exudate beneath cerebral arachnoid.	Hypertrophy of left ventricle. Heart empty.	A few ounces of serum in peritoneal cavity. Gastric mucosa intensely injected, but no ecchymosis. Numerous bright red inflammatory patches in small intestine, especially jejunum; walls infiltrated with serum; contents "dark bilious matter." Liver yellow and enlarged.	Local tumefaction due to serous infiltration.	Death after 18 hrs. Patient an alcoholic; condition of liver attributed to this cause. Contents of intestines may well have been altered blood.
4. Spaulding[15]	No clots found in heart.	Slight congestion and extravasation in brain and its membranes.	Pale and flabby, containing no clots. Lungs congested and edematous. One ounce of blood in each pleural cavity.	Stomach highly congested and partly filled with blood. Spleen and liver congested.	Considerable bloody extravasation in arm and right side as far down as groin.	Death after 38 hrs.

12. Home, Sir E.: Case of a Man Bitten by a Crotalus, Phil. Tr. Royal Soc., London, 1810, p. 75.

13. Pihorel: Observations sur la morsure d'un serpent à sonnettes, Jour. de physiol. expèr. et path., 1827, vii, 97.

14. Horner: Postmortem Examination of a Patient Who Died from the Bite of a Rattlesnake, Am. Jour. Med. Sc., 1855, xiii, 397.

15. Spalding: New York Med. Jour., 1884, xl, 66.

Among the cytolysins for the various parenchymatous cells, demonstrated to be present in all venoms, the most important in the pit viper venoms is undoubtedly the principle responsible for the multiple hemorrhages, the hemorrhagin of Flexner and Noguchi. These investigators have carefully studied the properties and mode of action of this substance. They say: "We look on hemorrhagin, therefore, in the light of a cytolysin for endothelial cells of blood vessels, the destruction of which is the direct cause of the escape of blood into the surrounding tissues." The actual giving way of the vessel wall and the escape of the blood has been observed under the microscope by many investigators. The most characteristic feature of crotaline poisoning, the decided tendency toward hemorrhage, is thus accounted for. The relative potency of different venoms in causing hemorrhages, which may depend on variations in the amount or quality of the hemorrhagin present, has been found by Flexner and Noguchi[8] to be as follows: If the cobra venom be taken as unity, then copperhead and moccasin venom are ten and rattlesnake venom one hundred times as potent. These figures show conclusively that the power to cause multiple hemorrhages is a common and decided characteristic of the pit viper venoms, since they are, in this respect, so much more powerful than the venom of the dreaded cobra.

Locally, in the subcutaneous and muscular tissues around the site of inoculation, the characteristically severe action of the crotaline venoms is due to many of the toxic principles already enumerated, the severity and extent of the lesions being caused by the concentration of the venom at this point. A proteolytic ferment is responsible for the softening and disintegration of the muscular tissues, and according to Noguchi[10] a principle analagous to hemorrhagin for the marked edema.

In summarizing the toxic action of the crotaline venoms, their ability to profoundly lower blood pressure, probably because of their direct selective action on the vasomotor center; their disintegrating action on the endothelium of blood vessels, resulting in the occurrence of multiple hemorrhages, and their antibactericidal effect on the blood serum, must be selected as their most dangerous properties. Their inhibition of coagulation, their functional depression of the whole cord and medulla, and the slight tendency exhibited by the two *Ancistrodon* venoms toward a selective action on the respiratory center, must be borne in mind.

PATHOLOGY.

Our knowledge of the macroscopic and microscopic lesions found after death from crotaline poisoning is limited and based almost entirely on experimental findings.

Certain gross pathologic changes have been found with great uniformity by various investigators, in the bodies of animals dying from venom intoxication. Locally, when the injection of venom has been subcutaneous, the muscles around the site of inoculation are found softened to the point of diffluence and dripping with extravasated blood. Evidences of antemortem pyogenic infection of the necrotic tissues are frequently observed. Petechial hemorrhages in the pericardium, endocardium, pleural cavities, peritoneum, mesentery, intestines, omentum, and even in the meninges, together with marked congestion of all the abdominal viscera, and less frequently of the lungs, are the lesions most frequently seen. The blood is generally found to be fluid and noncoagulable. Even in the small animals used experimentally antemortem, intravascular clotting is rare, except in cases in which the amount of venom injected was considerably in excess of the minimum lethal dose, and particularly when the injection was intravascular.

I have been able to find only four recorded autopsies in man, following death from the bites of American serpents, and of this number three have been previously commented on by Mitchell.[2] All are incomplete and would be worthless for the purpose of making any general deductions were it not for the similarity shown between the findings in actual and experimental cases of crotaline poisoning. The records of these necropsies are presented briefly in Table 1. Their great imperfection is evidenced at once by the single fact that the condition of the kidneys is not mentioned in a single instance. The first case, that of Home, is of little importance for showing the lesions of venom poisoning, death being undoubtedly due to secondary infection. It serves to emphasize, however, the destructive nature of the changes induced by septic infection of tissues previously devitalized by the activity of crotaline venoms. In the three remaining cases we are dealing with deaths due to the immediate toxic activity of the venom; the similarity of the lesions found, and their resemblance to those described in animal experiments, will be noticed. It seems worthy of mention that all the four rattlesnakes responsible for these deaths were in captivity and their bites were the results of careless handling.

Knowledge of the microscopic lesions in the various organs following venom intoxication is, so far as I know, dependent entirely on animal experiment. In those cases in which death has rapidly followed large doses of the venom the microscopic appearance of the parenchymatous cells has appeared to be little if at all altered. In more chronic cases of poisoning, however, especially where life has been prolonged for days, the cells of the various abdominal viscera show cytolytic changes; foci

of necrosis, often infiltrated with blood, make their appearance, degenerative changes in the myocardium are sometimes seen, and the kidneys may present the picture of acute hemorrhagic nephritis. Degenerative changes in the nerve cells of the cords of rabbits following somewhat prolonged poisoning by water moccasin venom, are reported by Langmann,[16] and Flexner and Noguchi[17] have demonstrated a true chromatolysis occurring in the isolated cells of several species of *Gastropod,* when treated with rattlesnake or moccasin venom.

SYMPTOMATOLOGY.

The clinical picture seen in actual cases of snake poisoning in man presents such wide variations that its intelligent presentation becomes a matter of some difficulty. The different factors determining the severity of the symptoms naturally have a decided bearing on the mortality and prognosis of the condition and will be given detailed consideration in that connection. The great differences in the toxic properties of the colubrine and viperine venoms are well shown by the characteristic differences in the symptoms of poisoning by the coral snakes and pit vipers, differences sufficiently great to necessitate their separate consideration. The symptoms of crotaline poisoning will be taken up first. It is not to be supposed, however, that all the symptoms enumerated below will occur in every case, for in any particular instance many or nearly all of them may be absent. The attempt has been made to consider all of the important symptoms present in the different cases studied and to indicate, in a general way, the frequency of their occurrence.

The symptoms of snake poisoning are both local and constitutional.

Local symptoms are always present in cases of crotaline poisoning even when evidences of constitutional disturbances are slight or entirely lacking. They are, in addition to the characteristic appearance of the wound, the usual manifestations of a rapidly spreading inflammatory process of severe grade, with markedly hemorrhagic and necrotic tendencies.

The appearance of the wound is, fortunately, almost pathognomonic. Its examination reveals the presence of two, occasionally only one, punctured wounds situated in the center of a rapidly spreading tumefaction. These are the fang punctures, and their size and the distance separating them, serve as a rough indication of the size of the snake causing the injury. The skin around the site of the fang wounds is occasionally found slightly abraded by the fine, retrocurved teeth of both the upper

16. Langmann, G.: Poisonous Snakes and Snake Poisons, Med. Rec., 1900, lviii, 40.

17. Flexner and Noguchi: Jour. Path. and Bacteriol., 1905, x.

and lower jaws. These abrasions are of absolutely no consequence even when made by the teeth of a very large snake. Rarely the fang punctures bleed actively either immediately or at some time after the bite; usually they only exude a bloody serum.

The great severity of the symptoms of the local inflammatory process set up by crotaline venom is characteristic. Pain is usually severe, especially after the swelling becomes extensive and in those cases in which prolonged tight ligation of the bitten part is practiced. The amount of pain caused by the bite itself is variable, probably depending on the size of the fangs and the amount of tearing of the tissues. Swelling is rapid both in its onset and spread, and in cases of any severity, where the lesion is on an extremity, it reaches the trunk within the first twenty-four hours. In some cases the tumefaction is considerable over the lateral half of the body receiving the injection, and in rare instances has been stated to have been general. In cases in which the lesion is on the face or neck the swelling is not only intense, but dangerous *per se,* because of the occurrence of edema of the glottis. This condition was present in a case reported to me by Dr. J. B. Ashford, of Water Valley, Texas. It was relieved by local blood letting, and the patient, an adult male, recovered. Swelling of a degree sufficient to cause spontaneous rupture of the skin is reported in several cases. The skin over the swollen parts is frequently so distended as seriously to endanger its vitality, presenting under these circumstances a peculiar glazed appearance. Discoloration is marked and extensive, spreading, in cases of bites on the extremities, well up on to the trunk. The color is that characteristic of extensive ecchymotic lesions, and may be uniform or patchy in its distribution. In many cases the skin immediately around the bite or over the whole of the bitten limb becomes covered with blebs and bullæ containing a blood-stained serum.

The amount of local necrosis following these extensive changes is variable; some cases escaping it entirely, although a slight superficial slough around the sight of the fang punctures is very common. In other cases, particularly those in which the tissues have had to withstand the devitalizing action of a prolonged ligation in addition to that of the venom, the local sloughing is much more extensive, involving deep as well as superficial tissues, frequently necessitating the loss of fingers or even in rare cases of a whole limb.

The constitutional symptoms present even greater variations in the degree of their severity than do the local manifestations, and every possible gradation is seen between cases resulting fatally in less than an hour and those in which constitutional disturbances is almost entirely

lacking. Usually, however, the prostration is alarming enough. Within a variable period following the bite, usually less than fifteen minutes, during which fright and terror may cause fainting, the patient experiences sensations of vertigo, an inability to use the limbs, and rapidly passes into a state of collapse. The symptoms of this stage differ but little from those of similar conditions due to more ordinary causes. The respiration may be either rapid and shallow, or slow and stertorous. The pulse is rapid, feeble and of very low tension. Blood pressure falls rapidly. The temperature is subnormal, the skin cold and clammy and covered with perspiration. Nausea is usually present and vomiting is a frequent occurrence. Power of voluntary motion is more or less completely absent, and the mind may be more or less clouded. Involuntary evacuations of the rectum and bladder may occur. In cases of ordinary severity, reaction from this primary collapse sets in usually within a few hours and the patient may rapidly pass from a condition exciting the gravest fears to one of comparative safety. This tendency to react promptly and effectively from a prostration of the utmost apparent gravity, irrespective of the line of treatment employed, is quite characteristic, and was first pointed out by Mitchell.[2]

In cases of greater severity progress is neither so rapid nor so favorable. Reaction may fail to occur, the patient sinking rapidly until death ensues.[18] In other cases[19] a tendency toward reaction is manifested by a fuller and less rapid pulse, a clearing of the mind, easier respiration, and a cessation of nausea and vomiting, only to be followed by the occurrence of a secondary collapse which usually proves rapidly fatal. This unfortunate accident has been caused in several cases by too complete and sudden removal of a ligature which was still segregating considerable of the venom from the general circulation. In other instances the cause of the secondary collapse is less obvious, although the result is the same. In the severe cases now under consideration many symptoms are present which are fortunately seen rarely, or only in modified form, in the average run of cases. Among these, the various manifestations of the hemorrhagic tendency induced by the venom are of great interest. In the average case this tendency is shown only by the purpuric discoloration of the skin and subcutaneous tissues of the bitten limb and adjacent portions of the trunk. In other instances the purpuric eruption may be general, and associated with more or less active epistaxis, bleeding from the mouth, hematemesis, hemoptysis, hematuria and hemoglobinuria and bleeding from the rectum, vagina, fang

18. See Cases 3, 4, 8 and 10, Table 2.

19. See Cases 5, 9, 12 and 13, Table 2.

punctures or the wounds made in treatment. A most interesting case, presenting practically all of these symptoms, is reported by Owen.[20] The patient, a young woman, was bitten on the ankle by a snake thought to have been a moccasin. All the hemorrhagic symptoms mentioned above were present except bleeding from the wound. No treatment is mentioned until about twelve hours after the bite, which may account for the severity of the case. The patient recovered in a week. Case 10 in Table 2 also shows conclusively how severe the hemorrhage may be. It is doubtful, however, if these symptoms are dangerous in themselves, and their greatest importance is found in their indicating the increased likelihood of hemorrhagic transudates at vital points. It should be borne in mind that hemorrhages in the heart, pericardium, medulla, brain or other viscera, may be the immediate cause of sudden death, or of various otherwise unaccountable symptoms which may serve to give a most unusual aspect to the clinical picture of a case.

A glance at the constitutional symptoms presented by the fatal cases collected in Table 2 will disclose many interesting manifestations referable to the nervous system. The preservation of a degree of mental clearness quite remarkable when the profound prostration present is taken into consideration, is characteristic in most instances, although in some cases an active delirium is present from the beginning. Delirium, however, is more frequently mentioned as a later symptom and in the great majority of cases is probably an indication of septic infection. Coma seems to be rare except as a terminal event in fatal cases. Great restlessness and jactitation are frequently mentioned; less often a paretic condition of the extremities. General convulsions were noted most often in children, as might be expected, and would seem to be of grave prognostic significance, every case in which they occurred ending fatally. Almost complete cutaneous anesthesia is mentioned in one case, and various paresthesias, such as a sense of constriction in the throat or chest, were noted several times. Symptoms referable to the cranial nerves are seen occasionally. Various disturbances of vision amounting to total blindness, paralysis of the ocular muscles, and ptosis have all been observed. During the stage of primary collapse, the pupil seems to be most frequently dilated, and may fail to react to light. As to whether these and other disturbances of functions are due to a direct action of the venom on the nerve centers involved or to the occurrence of minute central hemorrhages, it is difficult to say. In this connection the case reported by Bailie[21] is worthy of mention. The patient, an

20. Owen, F.: New Orleans Med. and Surg. Jour., 1867, xx, 207.
21. Bailie, A.: Med. Times, London, 1849, xx, 179.

adult male, was bitten on the ankle by a rattlesnake. A tendency toward hemorrhage was shown by the presence of blood in the stools and sputum, and the occurrence of a temporary ptosis, confined to the right side, might well have been caused by a small hemorrhage. A temporary amaurosis was also present in this case. Deafness of brief duration is mentioned in one case.

The findings in regard to temperature, pulse and respiration show little that is typical. When the primary collapse was at all severe the temperature, if mentioned at all, was stated to be subnormal. Fever is noted in a number of cases, but in most instances is undoubtedly septic in character rather than being reactionary, or due to disturbances of the heat regulating center. The pulse is usually stated to have been weak, rapid and lacking in volume, although a slow pulse was present in a few cases. The respirations were most frequently rapid and shallow, in a small number of cases slow and stertorous. The occurrence of hemoptysis has been noted. Pulmonary edema was present in a few cases. It is interesting to note that in Case 10, Table 2, it is definitely stated that the respirations continued after the heart ceased beating, an observation tending to support the statement previously made in regard to the lack of selective action of rattlesnake venom on the respiratory center. On the other hand the experimental findings in regard to the effect of *Ancistrodon* venoms on the respiratory center are strikingly borne out clinically by the case reported by Crum.[22] The patient, a young woman, about 20 years of age, was bitten on the ankle by a copperhead of medium size. Two hours later, the respiration ceased and had to be kept up artificially. This patient finally recovered.

Symptoms from the alimentary and genito-urinary systems are mainly manifestations of the hemorrhagic activity of the venom. Nausea and vomiting are present in almost every case of any severity. The character of the vomitus is rarely mentioned. The presence of blood is noted in some cases, in others it is stated to be bilious. Difficulty in swallowing or a complete inability to swallow was noted occasionally. The violent purging, with blood stained stools or even pure blood,[23] is more likely to be due to the action of the venom than the simple diarrhea occasionally noted, which may well be septic in character. Retention of urine requiring catheterization was present in a few cases. I have been unable to find the report of a single urinalysis in any of the cases

22. Crum, C. W. R.: Treatment of the Bites of Copperhead Snakes by Local Freezing Combined with Frequent Applications of Potassium Permanganate Solution, Jour. Am. Med. Assn., 1906, xlvi, 1433.

23. See Case 10, Table 2.

studied, beyond vague references to the amount passed and the amount of blood present. It is more than likely that investigation along this line would disclose the presence of a nephritis in cases of any severity and duration.

All that has been said above applies to the symptomalogy of crotaline poisoning exclusively. Knowledge covering the symptoms of colubrine poisoning in the United States must be based largely on reasoning from analogy, only seven cases being mentioned in the literature and these with a paucity of detail sufficient to make them practically worthless. It need only be said here, that bites by the coral snakes are followed by a characteristic absence of local symptoms and by a profound prostration, very frequently terminating fatally, probably from a paralysis of the respiratory center in the medulla. The symptoms presented by two fatal cases of coral snake bite will be found under Cases 14 and 15, Table 2, and it will be seen that there is no reason for believing that the action of the venom of these snakes differs essentially from that of other colubrine venoms. While cases of colubrine poisoning will undoubtedly continue to be so rare in this country as to be practically negligible, the following notes on the seven reported cases are appended for the sake of getting them recorded in medical literature. Of the seven cases only two have been previously mentioned in purely medical literature, one by Barringer[24] and one by Yarrow.[25] Stegner[1] collected six cases, including the two mentioned above. These were originally reported by True,[26] Coe[27] and Loennberg.[28] I am indebted to Dr. Menger, of San Antonio, for calling my attention to the case, mentioned by him in a paper read before the Scientific Society of San Antonio.[29] In a personal communication from Dr. C. L. Randall, of Altamonte Springs, Fla., mention is made of one other case, ending fatally.

Table 2 contains a tabular statement of the clinical data available in fifteen fatal cases of snake poisoning, three of which, Cases 1, 2 and 4 have been previously tabulated by Mitchell.[2]

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24. Barringer, P. B.: The Venomous Reptiles of the United States, with the Treatment of Bites Inflicted by Them, Tr. South. Surg. and Gyn. Assn., 1891, Philadelphia, 1892, iv, 283; also Gaillard's Med. Jour., 1892, lv, 7.

25. Yarrow, H. C.: The Recurrence of Symptoms of Poisoning After Snakebite, Med. News, Philadelphia, 1887, L., 623.

26. True: Am. Naturalist, 1883, xvii, 26.

27. Coe: Scient. Am., 1891, lxiv, 401.

28. Loennberg: Proc. U. S. Nat. Mus., xvii, 334.

29. Menger: Bull. Scient. Soc., San Antonio, 1905, i, 11.

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TABLE 2.—CLINICAL DATA IN FIFTEEN FATAL CASES OF SNAKE POISONING

Reference	Patient	Snake	Wound	Duration	Local Symptoms	Constitutional Symptoms	Treatment	Remarks
[illegible]	Man about 30 years	Captive rattlesnake	Hand, 2 bites, large wounds	Nine hours	Slight swelling and discoloration	Pulse and respiration rapid after rise to 130. Respiration rapid and labored, difficult deglutition, pupils contracted, swelling of lips	Ammonia, ligature and cupping of bitten parts, alcohol enemas, nitrate of amyl, injections of brandy, dashes of cold water, mustard plasters, effort to produce vomiting	Died in collapse, recovered from effects of bite
[illegible]	Adult male	Captive rattlesnake	Elbow	About 18 hours	Rapid swelling, redness and swelling	Rapid pulse, depression. Next morning young girl, cadaveric appearance of face, patches of dark bilious color, pulse thready, respiration labored, collapse, coma, death. Great prostration, voided albumen and pus, heart dilated, death	Ligature, scarification, alcohol, ammonia, carbonate of ammonia	Patient apparently relieved, but grew worse and died. Post-mortem findings as in Table 1
[illegible]	Adult male, about 30 years	Captive rattlesnake	Hand, over fourth and fifth metacarpal bones	Twenty-four hours	Pain and oppression in hand, then swelling and pain in arm, which extended to chest. Some discoloration	Chills, followed by excessive sensation of faintness in jugulars, giddiness and vertigo, general tremor, difficulty of speech, sense of constriction in throat, weakness, dullness, difficulty of deglutition, loss of use of right arm, slight syncope, which continued. Bleeding from gum, under jaw, difficult respiration, sensation, frequent deglutition, great anxiety and restlessness. Bloody urine, involuntary movements of right thumb and left leg, unconscious at the. Pulse ceased at one hour and was full and hard at the end	Ligature, cupping, incision, excision of bitten part, scarification, ammonia, alcohol, quinin, iodin, potassium iodid, chloroform, ether, hypodermic injection of brandy, and whisky, enemata of brandy and milk, and whisky, opium, and quinin	Patient afterward seemed better. Post-mortem findings as in Table 1
[illegible]	Male, about 40 years	Captive rattlesnake	Last phalanx, middle finger	About 3 hours	Jet of blood from wound, immediately following bite. Rapid swelling, discoloration, extending up arm	Pain, half hours after bite, pulse 80, soothing, strong, and full, soon pulse absent at wrist, ... Died in 3 hours after death	Immediate suction, excision of bitten part, cauterization, ligature, and application of ice, ammonia, alcohol, and whisky, chloride of iron, quinin, and strychnin	Spurt of blood may be considered injurious, because of a part of poison
[illegible]	Sash, cold	Rattlesnake, Texas	Near middle finger	Eighteen hours		Rapidly developed collapse, followed by arrest of digestion, severe vomiting, hiccough, and death	Ligature, in 20 minutes, but too late, whisky	Death was accelerated by sudden removal of ligature
[illegible]	Boy of 9 years	Copperhead	Little toe	Died in 24 hours	Rapid swelling. Second day entire limb and foot a shapeless mass, large vesicles over thigh, some of which burst, discharging a thin, offensive fluid, followed by gangrene of foot, extending rapidly, affecting entire limb and system	Second day, nausea, cold skin, vomiting, cerebral delirium, tongue dry and red, diarrhea. Third day, vomiting, convulsions, and death	Free incision, scarification, suction, use of whisky, and potassium iodid, subcutaneously, quinin, and ammonia	Death undoubtedly due to sepsis
[illegible]	Adult male	Captive rattlesnake, southern, large species	Slight bite on end of left ring finger	Thirty minutes	Quivering of bitten part	Sense of oppression, loss of appetite, death, convulsions, bursting of mouth and nose, death	Ligature, scarification, excision, cauterization, ammonia, alcohol, quinin, iodin, chloroform, ether, hypodermic injection of whisky, and brandy, and milk, stimulants generally	Death may have been due to wrong treatment
[illegible]	Negro boy, 7 years	Rattlesnake	Probably upper extremity	Three hours		Vomiting with bilious admixture, spasmodic movements, loss of senses, coma, death		
[illegible]	Boy 6 years, rough living, heavy, fifty pounds	Rattlesnake, about 6 feet	Back of left calf, 2 small punctures	Four hours, death occurred 2 hours after bite	Immediately around wound, but not to swollen, but upon body covered only with clothing, and also blood in urine, and discharged from bowels	Pain in four hours, pulse 120, respiration 40, skin cold, clammy, and covered with profuse perspiration, vomiting, and purging, involuntary passage of urine and feces, and death	Ligature, incision, and suction, whisky, and brandy, and milk, and ammonia, and quinin, and iodin, and chloroform, and ether, and hypodermic injection of

COMPLICATIONS AND SEQUELÆ.

The frequency with which crotaline poisoning is complicated by local or general septic infection, and the severity of these conditions when present, have received but scant attention in the literature. It is obvious that a marked predisposition to infection must be present. Locally, we are dealing with a greater or less amount of necrotic tissue, being gradually separated from the body by the usual process of sloughing. Those tissues in the neighborhood of the wound which have escaped death must of necessity be devitalized from the powerful and concentrated action of the venom, and in a large number of cases, from the effects of a prolonged ischemia induced by too light ligation. Great softening, edema, and infiltration with extravasated blood are also present. In addition to the general systemic depression which must follow such a severe intoxication, the positive reduction or total destruction of antibactericidal properties of the blood must be taken into consideration. It is little wonder, then, that septicemic and pyemic processes are so frequently observed clinically, but it is difficult to understand the scant consideration which has been accorded this phase of the subject in the literature. While the symptoms, course and treatment of these infections present nothing unusual, it must be pointed out that chills, high fever, full bounding pulse, and active delirium, stated to be present in so many cases, mean infection and not the venom intoxication to which they are, in the majority of instances, attributed. The frequency of this complication, and the necessity for guarding against it can not, in my opinion, be too strongly emphasized.

In addition to the infections beginning in the tissues around the wound and becoming localized there, or involving the body generally, there are undoubtedly various other infective processes, terminal or otherwise, which have escaped notice clinically. McFarland[40] observed a fatal pneumonia in one of the horses used in his attempt to prepare an effective anticrotaline serum, and pneumonia and other infectious diseases may reasonably be supposed to occur in man.

For the following report of a most interesting case, tetanus complicating snake bite, which so far as my reading goes is unique in medical literature, I am indebted to Dr. W. E. Hawkins, of Bayou Chicot, La. The patient, an adult male, was bitten on the thumb by a large rattlesnake. He received no medical attention, but did very well for about a week, when he first came under observation with well-developed symptoms of tetanus from which he died in two days. The fact that this

40. McFarland, H. J.: Some Investigations on Antivenene, Jour. Am. Med. Assn., 1901, xxxvii, 1597.

patient received no medical attention immediately after the bite renders it likely that the organism was introduced on the fangs of the snake rather than during the local treatment of the wound.

Deformity following snake bite is seen with considerable frequency in the form of fibrous ankylosis of the interphalangeal joints in cases in which the lesion is on a finger. Many such cases are reported. It would seem that extensive deformity might be reasonably expected to follow the cicatrization of the areas of extensive sloughing of superficial tissues and even of muscles, noted occasionally, but no such cases are reported. The extent and seriousness of this sloughing in some instances is well known in the case reported by Walker.[41] A man 35 years of age was bitten by a water moccasin on the dorsum of the hand over the third and fourth metacarpal bones. The accident happened on Sunday morning, the patient drank some whisky and tried to reach the house of a neighbor but fell, and lay all day in the sun, not being found until night. He was first seen by a physician on Wednesday, when the tissues around the bite were in a gangrenous condition. The sloughing became so extensive that the forearm was amputated, the patient making a good recovery. Permanent enlargement of the bitten limb is reported by Jones[42] in the case of an adult male negro bitten on the leg by a water moccasin. Mr. Wood of the Smithsonian Institution has reported to me a case of permanent hypertrophy of the thumb in a boy of twelve, bitten on this member by a small ground rattler, *S. miliarius*. Dr. C. W. Lindner, of Anthony, Fla., reports to me the following interesting and unusual case of deformity following the bite of a rattlesnake. The patient, a boy of ten or twelve, was bitten on the forearm a few inches above the wrist. When recovery was assured the arm was placed in splints and put up in a sling. The child's parents removed the splints, however, and a bow-shaped curvature of both bones resulted. This may have been a case of spontaneous fracture.

Anemia of considerable severity and duration has been noted as a sequel in a few cases. Crum[22] reports such a case following the bite of a copperhead. The patient, an adult female, had previously been in good health and ultimately made a good recovery.

A case of permanent although partial amaurosis is reported by Boseman.[43] The patient was a boy nine years of age bitten on the ankle by a ground rattler. There was considerable suppuration and sloughing

41. Walker, E. M.: Am. Jour. Med. Sc., 1858, xxxvi, 568.

42. Jones: Med. Rec., 1868-69, iii, 289.

43. Bozeman, N.: A Case of Amaurosis from Snake-bite. New Orleans Med. and Surg. Jour., 1849-50, vi, 739.

in this case and as the blindness did not develop until five or six weeks after the injury there is naturally a question as to whether it should be attributed to the direct action of the venom or to the resulting infection.

A belief in the possibility of a periodical recurrence of some of the symptoms of snake poisoning at varying intervals after the original injury, is firmly fixed in the popular mind. *A priori* reasoning would certainly seem to justify the categorical denial of such a possibility. Venom is an albuminous fluid, which from the very nature of things must, after its injection into the living body, either bring about the death of the organism or be itself speedily destroyed. It is therefore impossible to conceive of its remaining latent in the body to be the cause of future local or systemic disturbances. If, then, such occurrences have really been observed they must be accounted for on some grounds other than a latent action of the venom originally injected. Cases reported as recurrences in which the symptoms consist only of vague pains felt in the neighborhood of the wound at irregular intervals, may readily be due to any of the well known factors causing painful cicatrices. In these cases, however, the element of periodicity is lacking. I am perfectly willing to submit the evidence in the case and let the reader draw his own conclusions.

Yarrow[25] in 1887 collected all the alleged cases of recurrence up to that date and added two cases which had come under his own observation. I have found no additional cases worthy of mention reported since the time of Yarrow's article. Of the cases collected in this paper, those of Sweeney,[44] Stockbridge[45] and Coleman[46] have little to recommend them for consideration. Sweeney, for instance, reports a case, in which a condition suspiciously like an ordinary bone felon is attributed to the bite of a copperhead on the same finger thirty years perviously. Both of the cases which came under Yarrow's own observation are of considerable interest. From the original report[47] of the first there can be no doubt that there was considerable infection present. Of the subsequent history of this case Yarrow says: "The case of a photographer, bitten by a copperhead, . . . I have watched carefully from 1883 to 1886, the last attack commencing on May 30, the anniversary of his injury, and lasting over a week. His condition about the acme of the attack was as follows: Pulse quick; complains of general malaise; pain and stiffening in the bitten finger, which extends up the arm; surface

44. Sweeny: Cincinnati Lancet and Observer, 1860, new series, iii, 318.
45. Stockbridge: Boston Med. and Surg. Jour., 1843, xxix, 40.
46. Coleman: Virginia Clin. Rec., 1872-73, ii, 137.
47. Yarrow: Am. Jour. Med. Sc., 1884, new series, lxxxvii, 422.

of hand shows bluish mottling, with lines of redness extending as far as the shoulders along the lines of the lymphatics. He had slight chilly sensations, and some fever. Obliged to quit work, as he could not concentrate his attention to it. Has taken nothing but whisky and quinin. These notes were read to him, and he stated that they represent fairly his condition at each recurring period since the bite." The second case was that of an adult male bitten on the finger by a coral snake *(Elaps fulvius)* in 1882. Each subsequent year at approximately the anniversary of the bite a small abscess formed in the bitten finger, from which the nail would be lost.

The case of Piffard[48] is undoubtedly the most interesting in the literature. It is reported in great detail. At the first examination of the patient there was noted a tendency toward contraction of the flexor tendons of the right forearm and the presence of a vesicular eruption on the skin between the thumb and index finger of the right hand. Inquiry elicited the information that the patient, a young woman of nineteen, had been bitten on the thumb by a rattlesnake several years previously. At the time, in addition to the usual symptoms there had been a contraction of some of the flexor tendons and an inability to extend the hand. At regular periods of three months the patient had noticed the appearance of a vesicular eruption over the metacarpal bone of the thumb, associated with a "beating" pain and contractures of the flexor tendons. The woman's husband confirmed her statement and Piffard himself observed attacks occurring consecutively in March, June and September and on several subsequent occasions. The interval between attacks gradually became longer, and when last seen the patient had had no attacks during a period of seven or eight months. The total duration of these strange phenomena was over ten years.

In this connection, it may not be amiss to transgress the limitations of the subject to American serpents, in order to mention the very interesting case of Demeurat.[49] His patient was a young woman 26 years of age, who was bitten in May, 1824, by the common European viper, *Vipera berus*. In addition to the more usual symptoms a bullous eruption made its appearance on the skin of the bitten part and did not entirely disappear until November of the following year. In the last part of May, 1826, and at about the same time for 39 consecutive years,

48. Piffard, H. G.: Periodical Vesicular Eruption Following the Bite of a Rattlesnake, Med. Rec., N. Y., 1875, x, 62.

49. Demeurat: Observations d'accidents developpés à la suite d'une morsure de vipère, Gaz. hebdom. de méd., 1863, x, 736.

a similar eruption made its appearance, lasting about six weeks, and preceded by lassitude, anxiety, nausea, headache, and other evidences of constitutional disturbance.

DURATION.

Like everything else connected with the subject, the duration of the illness following snake bite is subject to the widest variations. In the great majority of cases recovery from the constitutional disturbance is complete in two or three days and many times in a few hours. The entire restoration of the tissues around the bite to a normal condition usually takes longer, the exact time taken depending mainly on the amount of necrosis and sloughing and whether or not infection occurs. Tuten[50] reports a case following the bite of a rattlesnake, in which the ulcerated surface left after the separation of the sloughs was over a year in healing. There can be no doubt that the cases of prolonged illness so frequently reported are septic in character, and rarely if ever due to the primary action of the venom. The duration of the fatal cases shows much less variation, although largely influenced by the same factors. Of the seventy-eight fatal cases in the series the time of death was noted with considerable accuracy in fifty cases. An analysis of these cases is presented in Table 3, and for comparison the findings given by Fayer[51] in a similar analysis of sixty-five cases of cobra poisoning. The rather striking similarity is of considerable interest.

TABLE 3.—DURATION OF FIFTY FATAL CASES OF POISONING BY AMERICAN SNAKES COMPARED WITH THAT OF SIXTY-FIVE CASES OF COBRA POISONING.

Duration.	Series of 50 American cases.		Series of 65 cobra cases.
	No. of cases.	Per cent.	Per cent.
Less than one hour	8	16	..
One to six hours	13	26	..
Less than six hours	21	42	46.4
Six to twenty-four hours	18	36	32.5
Less than twenty-four hours	39	78	78.9
Second day	4	8	..
Third to seventh days	4	8	..
Nine days	1	..	..
Seventeen days	1	..	..
Over one month	1	..	..
Longer than twenty-four hours	11	22	21.1

CAUSE OF DEATH.

The action of coral snake venom, as shown in the few recorded cases of bites by these snakes, is sufficiently like that of other colubrine

50. Tuten, J. G.: Jour. Am. Med. Assn., 1897, xxix, 896.
51. Fayer, quoted by Noguchi (8).

venoms, which have been most carefully studied, to render reasonable the belief that death in these cases is usually due to paralysis of respiration.

In crotaline poisoning, however, the cause of death can not be stated with such certainty, and it evidently varies with the time elapsing before its occurence. Cases terminating fatally within a few minutes of the injection of venom are fortunately very rare, but do undoubtedly occur. Roberts[52] reports the case of a boy seven years of age bitten twice by a rattlesnake, once on the hand and once on the cheek, below the eye. The child screamed and pitched forward and was dead before an eye witness of the affair could reach him. Blackwood[53] reports a death occurring within ten minutes in the case of a girl three years of age, bitten on the eyebrow by a large rattlesnake. Unfortunately the reports of these cases are so extremely meager as to preclude the possibility of making deductions concerning the cause of death, from an analysis of the symptoms presented. The possibility of death from shock must be considered, particularly in such a case as that of Roberts. Immediate intravascular thrombosis or the occurrence of hemorrhages in the heart or central nervous system would, of course, afford a satisfactory explanation. In Blackwood's case, however, the blood was found after death to be perfectly incoagulable. As I have stated, I am very skeptical in regard to the possibility of crotaline venom causing immediate intravascular thrombosis in man, with the possible exception of cases similar to the two under discussion, in which, it will be observed, both patients were small children, and the location of the bite was extremely vascular.

Death, in the great majority of cases, occurs in the first twenty-four hours, usually during the primary collapse, in a few cases in a state of secondary collapse to which reference has been made. In these cases sudden death may be due to hemorrhage at vital points and the possibility of fatal termination from suffocation, in cases in which the bite is on the face or neck, should be borne in mind. In most instances, however, both experimental and clinical findings point to a combination of general nervous depression and circulatory failure, due to lowered blood pressure, and resulting in secondary respiratory failure, as being responsible for the fatalities. The greater prominence of primary respiratory failure in cases of *Ancistrodon* poisoning has been pointed out.

In those cases in which death occurs days, weeks or even months after the bite, there can be no doubt that sepsis or some of its complications is responsible. It is interesting to note that of the seventy-eight

52. Roberts, J. C.: South. Pract., 1888, x, 374.
53. Blackwood, W. R. D.: Med. Reg., Philadelphia, 1888, iii, 272.

fatalities in the series, eight may be definitely stated to have been due to sepsis. This would indicate that infective processes are responsible for 10.2 per cent. of the fatal cases, probably an underestimate when we take into consideration the lack, in such a large number of cases, of clinical details sufficient to positively exclude sepsis. Rarely, possibly, death in these cases may be due to the necrotic lesions in the various viscera, particularly the liver and kidneys.

DIAGNOSIS.

The question of diagnosis rarely comes up for solution, the history of the case being usually complete. The venomous or innocuous character of the snake causing the injury will require decision in some cases. If the reptile has been killed its identification may be readily made by looking for the characteristic points considered fully in Part I. If the reptile can not be examined dependence must be placed on the appearance of the wound, which also has been previously considered under symptomatology. Only in exceptional cases will the question as to whether the lesion is due to snake bite or some other form of injury, need solution. The wound, in these cases, may be inflicted in the dark, or persons may be bitten when entirely alone, and found only after death, or unconsciousness has supervened. Here, again, the pathognomonic appearance of the wound, together with the presence of ecchymosis and swelling locally, the profound general collapse, and the subnormal temperature will aid in making a correct diagnosis. A case in which the diagnosis lay between erysipelas and snake bite is reported by Thomas.[54] The patient, a boy of four or five years received an injury on his foot while walking through a stubble field known to have been infested with rattlesnakes. The wound consisted of two scratches. Death occurred on the third day, following enormous swelling of the limb, nausea, vomiting, collapse, and subnormal temperature. The case was diagnosed, correctly in my opinion, as one of snake bite.

MORTALITY.

The mortality from the bites of American serpents has never been satisfactorily determined. Mitchell,[2] in 1860 stated that in 57 cases of rattlesnake bite mentioned in the literature, five patients died. This would represent a mortality of 8.7 per cent. Elzey,[55] whose opinion is often quoted, merely estimated that in 15 per cent. of cases of rattlesnake bite in adults, the patients would die, if left untreated. Barringer[24] stated

54. Thomas, J. T.: Med. Rec., New York, 1890, xxxvii, 123.

55. Ellzey, M. G.: The Venomous Snakes of the United States and the Treatment of Their Bites, Virginia Med. Month., 1884-85, ii, 249.

his belief that the mortality from rattlesnake bite would not exceed 10 per cent. and from copperhead bite 1 per cent. The mortality from water moccasin bite, he thought, would fall below even this last figure. There were 78 fatal cases in the total of 740 which I have collected, a mortality of 10.5 per cent. This figure represents the mortality of all species combined, and in my opinion may be accepted as representing with considerable accuracy the actual mortality attending snake bite in the United States, the number of cases on which it is based being considerable, and having been collected from sufficiently varied sources. As tending to prove the accuracy of this rate, it may be stated that the mortality rates for cases collected from the literature and from various private sources were, respectively, 10.2 per cent. and 10.7 per cent., a variation of only 0.5 per cent. The mortality rate for the different species will be given later in considering the effect of species on the prognosis.

PROGNOSIS.

That an extreme degree of variation in the severity of the symptoms of snake poisoning as seen clinically, is one of the most characteristic features of the condition, has been frequently mentioned previously. It is obvious then, that intelligent prognosis in these cases must be based on a knowledge of the factors determining this variation. These may be stated as follows:

1. The amount and toxic quality of the venom injected.
2. The location and character of the injection.
3. The age, sex and resisting powers of the patient.

It will be readily appreciated that these factors influence the outcome of a case mainly because on them depends the rapidity and amount of venom absorption by the system, in proportion to the weight of the patient.

The amount of venom injected in actual cases of snake bite will depend largely on the size of the snake, the length of time during which its supply of venom has been accumulating, and the perfection with which all the muscular acts concerned in the bite are carried out.

The size of the snake naturally determines the size and capacity of the poison glands and their ducts. This is well shown by the figures given by Mitchell,[2] who compared the length and weight of three rattlesnakes with "the amount in water drops which a single gland in each snake was capable of containing." The findings were as follows:

No. 1—Length, 18 inches; weight, 9½ ounces; capacity of gland, 11 drops.
No. 2—Length, 25 inches; weight, 18 ounces; capacity of gland, 19 drops.
No. 3—Length, 49½ inches; weight, 3 pounds 2 ounces; capacity of gland 29 drops.

In the introduction to their later publication Mitchell and Reichert[1] mention a specimen of *C. adamanteus,* eight and one-half feet in length, which at one bite ejected about one and one-half drams of venom, which of course represented the contents of both glands. These brief statements show conclusively that the chances of a large dose of venom having been injected increase proportionately with the size of the snake causing the injury.

On the other hand, the amount of venom in the glands of a snake of only average size may be greater than the amount in the glands of an unusually large reptile which has recently made use of its fangs. The exact rate at which the poison is elaborated is not known, but it is undoubtedly a comparatively slow process not at all comparable to the secretion of saliva. Mitchell[2] mentions a rattlesnake fifty-three inches in length which ejected about fifteen drops of venom from each fang on one day and only one or two drops on the day following. The great difference in the danger attending a bite by this particular reptile, on the two different days, is obvious.

Certain factors in connection with the perfection of the bite are of the greatest importance. In an absolutely perfect bite, the snake succeeds in injecting the full contents of both glands to the depth of the full length of the fangs. In many actual cases this degree of perfection is not attained. No venom at all may be injected; because of the absence of both active fangs, and the immature condition of the first reserve fangs, or because of an insufficient erection of the fangs, causing their convexities rather than their points to strike the bitten surface, thus bending them back into the animal's own mouth into which the venom harmlessly escapes. When the bite is located on a small member like a finger the fangs may straddle the bitten part, or may completely perforate it, in either of which events, of course, little or no venom would enter the tissues. Any of these conditions may affect only one fang, causing the dose of venom to be decreased by one-half. There can be no doubt that in many actual cases, the bite is inflicted with only one fang. Thus in seven bites inflicted on dogs Mitchell[56] found that the wound had been made by two fangs in four cases and by only one in three cases. Numerous cases are reported in which the wound showed the mark of only one fang. Hopkins[57] reports the case of a child bitten three times on the calf, by a copperhead; of the three wounds two were caused by one fang only. It is possible, also, that in some cases there

56. Mitchell, S. W.: On the Treatment of Rattlesnake Bites, with Experimental Criticisms of the Various Remedies Now in Use, N. Am. Med.-chir. Rev., 1861, v, 269.

57. Hopkins: Med. Rec., 1889, xxxvi, 431.

may be an escape of venom around the fang instead of through the poison canal, because of some inaccuracy in the approximation of the duct from the gland and the upper orifice of the poison canal of the fang, in which case, of course, the amount of venom would be correspondingly decreased.

It will be readily seen that all the factors which have been given consideration above affect the prognosis because they have a most direct bearing on the dose of poison administered, and therefore, are of the greatest importance. Unfortunately the most important point, the probable amount of venom in the glands, will be known only in very exceptional cases, as when the snake has been for some time in captivity and the time elapsing since a previous bite is known. An examination of the wound, however, will frequently give a clue as to the perfection of the bite and, therefore, some idea as to whether or not the full contents of both glands could have been injected. In addition, if the marks of both fangs are present, the distance separating them gives a rough idea of the size of the snake. In cases in which this is known more accurately it becomes a most important factor in the prognosis.

The toxic qualities of the venom injected are, of course, of very considerable importance in determining the outcome of a case. These vary as has been pointed out, with the species of the snake, but it is doubtful if the season of the year determines any increase or decrease in the toxicity of the venom, as is frequently seen stated. It must be borne in mind, however, that the species not only affects the toxic properties of the venom, but to a large measure the size of the snake, and therefore the amount of venom injected. For this reason the mortality following the bites of the pit vipers does not vary with the species as might be expected from the relative toxicity of the venom as shown for guinea-pigs. In Table 4 are given the findings in 624 cases of snake bite in which the species was known more or less definitely.

TABLE 4.—EFFECT OF THE SPECIES OF THE SNAKE MORTALITY IN 624 CASES.

Genus or species.	Number cases.	Number fatal cases.	Percentage mortality.
Rattlesnakes, genus *Crotalus*	38	6	15.7
Rattlesnakes, genus *Sistrurus*	20	0	0
Rattlesnakes, genus not given	350	42	12
All rattlesnakes	408	48	11.7
Copperheads	97	5	5.1
Water moccasin	53	9	16.9
Crotaline snakes, species not given	58	1	..
All species	616	63	10.2
Coral snakes	8	6	75.0
All crotaline snakes	624	69	11.0

A more detailed study of these figures is necessary and interesting.

It is unfortunate that the exact species of rattlesnakes is not more frequently mentioned in reporting cases, for practically nothing is known concerning the relative toxicity of the venoms of different species and some light might be thrown on the subject from practical sources if the number of cases were large enough. The small size of the ground rattlers as compared with that of the larger species of *Crotalus*—and it is the larger species which are responsible for most of the bites—readily accounts, however, for the different mortality rates shown in Table 4. There can be little doubt that bites by the ground rattlers, particularly *S. miliarius,* are practically never fatal to adult man except, possibly, through septic complications, and the species of this genus are our least dangerous poisonous snakes. The mortality rate given for all rattlesnake cases, 11.7 per cent. is, in my opinion, based on a sufficiently large series of cases to be accepted as approximately correct.

There were five fatalities in the 97 cases of copperhead bite in the series, representing a mortality rate of 5.1 per cent. Of the 5 fatal cases, 2 were in children, both being reported by Kunkler. The first case,[58] occurring in a boy of nine years, received no treatment. The fatal termination in the second case, a boy of six years, was undoubtedly due to sepsis.[59] The remaining three cases were reported to me, two by Dr. C. W. R. Crum, of Brunswick, Md., the other by Dr. C. B. Turner, of Bluemont, Va. All the patients were adult males and in every case the amount of bad whiskey taken by the patient was considered by the reporter to have been a decided factor in the fatal outcome. These facts make it clear that the prognosis in copperhead bite is very good, even in children, and it is very doubtful if the bite of this specie is ever fatal to adults in uncomplicated cases. Such a finding is of interest when the greater toxicity of this venom, as compared with that of the rattlesnake, is considered, and it is to be explained on the ground of the much smaller average size of this species. There seems to be some reason for believing that the fangs in the copperhead are both absolutely and relatively smaller than in the other pit vipers and this fact would, of course, assist in explaining the comparatively slight danger of its bite, the injection of the venom being more superficial.

The mortality of 16.9 per cent. in the 53 cases of water moccasin bite in the series points at once to the dangerous character of this snake, and bears out in a suggestive way the experimental findings in regard to the toxicity of its venom. That the mortality is not greater is again due, in a large measure, to the question of size. The water moccasin, while

58. Kunkler, G. A.: Med. Counselor, Columbus, 1855, i, 481.
59. See Case 6, Table 2.

averaging much larger than the copperhead, certainly never attains the large size of some of the larger species of Crotalus. Ellzey[55] considers this reptile our most dangerous snake, an unenviable distinction which must, in my opinion, be accorded to *C. adamanteus*. In a large series of cases, however, the mortality following moccasin bite would certainly exceed that of all rattlesnake bites taken collectively. It is fortunate that the habits and somewhat limited distribution of this species make its bite an infrequent occurrence.

The frightful mortality following the bites of the coral snakes, 75 per cent., is based on a number of cases entirely too small to be of great accuracy, and is undoubtedly excessive, since it exceeds that given for cobra bite, 25 to 45 per cent. (Calmette). It serves, however, to emphasize the dangerous character of this snake which was long considered to be almost harmless to man, and the necessity for its correct differentiation from the non-venomous species which simulate its general appearance. Being small snakes the dangerous nature of coral snake venom, a characteristic colubrine feature, is made evident.

All those factors in the prognosis which have been considered have had to do with the amount and toxic quality of the venom injected. The factors contributed by the location and nature of the injection, and the resisting powers of the patient now claim attention.

TABLE 5.—EFFECT OF LOCATION OF THE BITE ON MORTALITY IN 347 CASES.

Location of bite.	Number cases.	Number fatal cases.	Percentage mortality.
Finger	61	6	9.8
Hand and wrist	67	13	19.0
Arm	11	2	18.1
Upper extremity, exact location not given	9	4	....
Upper extremity, total cases	148	25	16.8
Foot and ankle	123	7	5.6
Leg	55	8	14.5
Lower extremity, exact location not given.	5	1	....
Lower extremity.	183	16	8.7
Extremity, exact location not given.	4	..	....
Both extremities, total cases	335	41	12.2
Throat	1	0	....
Tongue.	1	1	..
Scalp.	2	0	..
Cheek.	3	3	...
Eyebrows.	1	1	....
Lip.	2	1	...
Vulva.	1	1	....
Penis.	1	0	..
Head and trunk, total cases	12	7	58.3
All locations, total cases	347	48	13.8

A study of the varying mortality rates for bites on different portions of the body, shown in the analysis of 347 cases presented in Table 5,

discloses many points of considerable interest. It has long been known that bites on the trunk and head are more dangerous than those on the extremities, and this is confirmed by the mortality rates given in Table 5, which are, respectively 58.3 per cent. and 12.2 per cent. The number of cases of bites on the head and trunk is so small, that the rate given, may well be inaccurate and is probably somewhat excessive. The great danger of bites here as compared with those elsewhere is clearly demonstrated, however. The reasons for such a difference are to be looked for in the greater vascularity of the head and neck, which determines a more rapid absorption and an increased danger of the venom being injected directly into a blood vessel, and the difficulty of taking effective measures by means of ligatures to localize the venom at the seat of injection. It is fortunate that the bite is located on the head or body in such a small number of cases, 3.4 per cent. in the 347 cases in the series.

The striking difference in the mortality of bites on the upper and lower extremities is, so far as my knowledge goes, here pointed out for the first time. It will be seen that the rate for the upper extremities, 16.8 per cent., is practically double that for the lower, 8.7 per cent. The difference in the rates for the hand and wrist, and foot and ankle, 19.0 per cent. and 5.6 per cent. respectively, is even more striking. Therapeutic measures intended to limit the amount of venom absorption may be applied with equal effectiveness to either extremity and the reasons for the greatly decreased danger attending bites on the foot and leg must be accounted for on other grounds. There can be no doubt that the more active circulation of the upper extremity, the greater number and prominence of the superficial veins, the vascularity of the thenar and hypothenar eminences, and the flat shape of the hand, allowing a firmer grasp by the snake, are all of importance, determining, as they do, increased rapidity of venom absorption, greater likelihood of intravenous injection, and increased dosage.

Different observers have stated that bites on the fingers are particularly dangerous because the fangs are more likely to be driven deeply into the tissues. This statement is not borne out by the mortality rate of 61 cases of such bites, which was 9.8 per cent., the lowest rate for any location on the upper extremity. This may be readily accounted for by considering the size and shape of the finger, not only making successful local treatment very easy, but tending to decrease the amount of venom injected, because in many cases one or both fangs may fail to penetrate at all, passing harmlessly to the side, or may completely perforate the member.

In connection with the effect of location of the bite on prognosis

the observations of Rinn[60] in his exhaustive thesis entitled, *Le Venin des Viperes Francaises,*" are of interest. Translated, he says: "Considered from the viewpoint of the influence of the location of the bite, our observations give the following results:

Place bitten.	Number cases.	Fatalities.	Percentage mortality.
Fingers	11	1	9.0
Webs between fingers	3	1	33.0
Hand	4	2	50.0
Foot, maleolus and leg	8	3	36.0
Breast, forehead, abdomen	3	3	100.0

"Bites on the fingers are perhaps the most benign because it is very easy to express the venom by suction and pressure."

That the age of the patient would have a marked influence on the mortality might be expected, since the dose of venom per kilo of body weight is of course greater in reverse ratio to the weight of the patient. In Table 6 the mortality in 129 cases of snake bite in children is given. The figures here presented are of very considerable interest, but require no further elucidation.

TABLE 6.—MORTALITY OF 129 CASES IN CHILDREN.

Age of patients.	Number cases.	Number fatal cases.	mortality. Percentage
Children 1 to 5 years, inclusive	23	6	26.0
Children 6 to 10 years, inclusive	36	6	16.6
Children 11 to 15 years, inclusive	51	5	9.8
Children, exact age not given	19	7	36.8
Total number of cases in children	129	24	18.6

A study of the 372 cases in which the sex of the patient is mentioned, with the idea of determining what if any influence sex has on the mortality, has given results which are accounted for with some difficulty. Thus there were 49 fatalities among 277 cases in male patients, representing a mortality of 17.4 per cent., and 10 fatalities among 95 cases in female patients, a mortality of 10.5 per cent. Common sense teaches that resistance to venom intoxications must be approximately equal in the sexes, kilo for kilo of body weight, and this being accepted as true a lower mortality among male patients would naturally be expected. The findings as given must be accounted for on other grounds, therefore, or accepted as tending to show unreliability in all the statistics presented. In my opinion, several factors may reasonably be advanced

60. Rinn, P.: Le venin des vipères françaises. Diss. Faculté de médecine de Nancy, 1905-06, p. 90.

as tending to account for the discrepancy. Thus a fatal termination following bites inflicted by snakes in captivity is very frequent and although a considerable number of such cases are reported only two patients were females, and of these one died. Of the six fatal coral snake cases four patients were males and in two the sex was not stated. The two cases which recovered were males. Finally, it is reasonable to suppose that bites in women would be inflicted more frequently through the clothing, and under such circumstances as regards proximity to civilization, etc., as to render likely the small size of the snake and the availability of appropriate treatment.

The nature of the injection is a factor which plays a most important part in determining the outcome of cases. In the great majority of instances the injection is into the subcutaneous areolar tissues. In a few cases, however, the venom from one or both fangs is discharged directly into the blood stream. Such occurrences, although rarely recognized, are probably partly responsible, as has been pointed out, for the large mortality of bites around the head and neck or on the upper extremity, and such a mode of injection may well have been responsible for some of the very rapid deaths already discussed. In only two cases in the series was there definite evidence pointing towards an intravenous injection of venom. One of these is the case reported by Post[61] and the other is a case mentioned in a personal letter from Dr. John Fitzsimon, of Castroville, Texas. The patient was bitten on the wrist, "on a vein," and died within two hours.

TREATMENT.

A rational and effective treatment of snake bite is to be arrived at only by keeping constantly in mind the clinical nature of the poison, the nature of the pathologic changes induced by it, and the mode of its administration. It may be stated in the beginning that the majority of patients will undoubtedly recover without any treatment, for the simple reason that the amount of venom injected is not a fatal dose. In individuals who have received an amount of venom equalling or exceeding the fatal dose, the rendering of any material aid to the patient is a most difficult matter, requiring very nice judgment and discrimination. In snake poisoning as in many other conditions, the mere length of the list of drugs and other therapeutic procedures recommended as specifics in the treatment of these cases is proof positive of their utter worthlessness in most instances, and a consideration of most of these procedures would be of no interest save for the light it might shed on the

61. See Case 4, Table 2.

ever present tendency of the medical mind to render to its own skill and ability that homage which, all too often, belongs to Nature. Indeed, the list of remedies which have been used in cases of snake bite, includes almost everything conceivable, from Calmette's antivenomous serum to local applications of cloths saturated with urine, or poultices made by splitting open living chickens.

It is customary to take up the consideration of the treatment of snake poisoning under the two general headings of local and general or systemic treatment. Such a classification of the subject is at least open to the criticism that it tends to inculcate the belief that there is a general or systemic treatment, a belief, which so far as the efficacy of any of the means ordinarily employed is concerned, is open to serious doubt. Nevertheless, this division will be followed here, if for no other reason than to emphasize the overwhelming importance of the local treatment. For there can be no doubt that the main therapeutic indication is the prevention of the systemic absorption of a fatal dose of venom from the amount, be it large or small, contained in the tissues immediately around the wound, and if this cannot be met the outlook for the patient, no matter what line of general treatment is employed, becomes exceedingly grave. The limitation and retardation of absorption, by ligatures and other means, and the removal or destruction of the injected venom, are thus the objects of all local treatment.

The absolute prevention of all absorption is probably impossible. Experiments on rats have demonstrated that the animals would die following venom inoculation at the end of the tail, even when this member was amputated within one minute. The control of the circulation in the bitten part, necessary to prevent absorption may be effected by the use of local freezing mixtures or ligatures. Of these the former may be dismissed with brief mention. The ethylchlorid spray has been used and recommended in this country by Crum[22] in conjunction with the use of ligatures and potassium permanganate. Aside from its anesthetic action, I doubt whether it would bring the circulation to a standstill to a sufficient depth to be of much value in cases in which the fangs had penetrated to any great degree and unless kept on hand with an eye to its use in just such emergencies it is a drug which would be rarely obtained under the conditions usually existing where cases of snake bite are most likely to occur. On the other hand, in bites on the head and body, the use of some such procedure is almost the only means at our command. Ligatures, however, are always easily improvised and, since the great majority of bites are on the extremities, easy

of application. Indeed so important are they in the management of these cases, that a detailed consideration of their use becomes necessary.

The amount of good to be gained by the use of ligatures will depend largely on the length of time elapsing between the receipt of the injury and the beginning of treatment. In cases seen early the complete control of the circulation during the preparation for the other local treatment, is certainly indicated. This is best accomplished by the use of a series of ligatures between the bite and the heart, at least one of which should be applied to that segment of the limb containing one bone. The danger of this treatment, if long continued, even with perfectly normal tissues, should be borne in mind, together with the devitalizing local action of crotaline venoms, and the ligatures partially relaxed as soon as practicable. There can be no doubt that many of the cases of extensive local gangrene, following snake bite, should be attributed as much to the prolonged ligation as to the necrotic activity of the venom. In cases seen first after some little time has elapsed, the local swelling being marked and constitutional symptoms already in evidence, complete control of the circulation is of doubtful utility. On the other hand, ligatures so applied as to impede the return flow of blood and lymph, render absorption more gradual, prevent the complete overwhelming of the system by large doses of venom, rapidly absorbed, and yet do not add greatly to the danger of extensive local necrosis. Ligatures applied in this way should replace those completely stopping all circulation, as soon as practicable. It is impossible to lay down fixed rules in regard to the time of beginning the removal of the ligatures and the rapidity with which it should be accomplished; this must be governed by the conditions present in each case. The greatest caution is necessary, however, for in several cases the fatal termination has been attributed to too sudden removal of all impediment to absorption, permitting a large amount of venom to gain access to the general circulation. It is probably safest to begin by intermittently relaxing the ligature nearest the heart, letting it become looser and looser until it is entirely removed. The other ligatures may then be taken off in the same manner.

It is obvious that, having absolutely controled, or at least limited the rapidity of venom absorption by the means just considered, it next becomes necessary to eliminate or destroy as much of the injected venom as possible. Here we may consider separately the various procedures aiming at the absolute removal of the venom, and those aiming at its destruction *in situ*.

Amputation of a bitten limb immediately following the receipt of the injury, or even after a considerable interval if tight ligation had been practiced, would undoubtedly rid the system of the necessity of coping with the larger portion of the injected poison. Such a procedure would be justified and probably often life-saving in those cases in which the whole contents of both poison glands of a large snake have been injected the full depth of the fangs, particularly if the lesion were in the fleshy part of the hand or on the forearm or calf of the leg. Unfortunately it is only under the most exceptional circumstances that any idea as to the amount of venom injected can be obtained. For this reason primary amputation of a large limb will probably be rarely if ever resorted to and I know of no case in which it has been done. On the other hand, the removal of a toe would seem to be entirely justified if it could be done immediately following the injury, or later, if there were reason to suppose most of the injected venom had been confined by ligation. Even in the case of a finger, amputation should certainly be considered under similar circumstances, in any case in which the species or size of the snake or nature of the wound made a guarded prognosis advisable. As has been pointed out previously, bites on the finger are likely to be followed by ankylosis of the joints, contractures of the tendons, or both, resulting in an amount of deformity greatly impairing the usefulness of the member, and little hesitancy should be felt in removing the part if the seriousness of the case seems to demand it.

Immediate amputation having been decided against, the correct surgical treatment of the wound becomes of the utmost importance. Deep excision of the bitten area if sufficiently prompt and radical, probably removes the major portion of the poison. In many locations, however, this treatment is impossible, and cases are seldom seen early enough to render it sufficiently valuable to compensate for its obvious disadvantages. The amount of venom removed by labial suction is probably excessively small, because it is very doubtful if the fang punctures remain patent. Suction following free incision, on the other hand, may be reasonably supposed to facilitate the escape of venom, if the treatment is instituted immediately. Later, after the diffusion of the venom in the tissues, little can be hoped from such a procedure, and the increased danger of infection attending it should contraindicate its employment. The most usual surgical treatment of these cases has been to make two deep incisions through the fang punctures with the idea of allowing the escape of some venom and in order to bring into more intimate contact with the remainder, the drugs used in the attempt at its chemical destruction. As recently pointed out by Martin and Lamb,[7]

ideal treatment requires more than this. The direction of the fang wounds is unknown, the skin may have been pushed or pulled some distance out of its normal position before the fangs penetrated the subcutaneous tissues, or the muscles, when penetrated, may have been in an entirely different position from that present when the wound comes under examination. Because of these facts, the writers mentioned recommend a careful and extensive dissection of the wound. In my opinion, the amount of benefit to be derived from these or any other local measures aiming at allowing the escape of the venom will depend on the degree to which the venom has been taken up by and become diffused through the tissues, which of course will depend on the length of time elapsing before treatment is begun. Most cases of snake bite are first seen by the physician after an hour or more of more or less complete ligation, with the portion of the limb distal to the ligature already considerably swollen and discolored. Under such circumstances, a dissection of the wound, and even free multiple incisions throughout the swollen area, together with such measures as kneading and massaging the part, and its immersion in warm, mild antiseptic solutions, to promote hemorrhage and the escape of serum, offer the greatest likelihood of eliminating most venom. While it is very unlikely that the amount of venom gotten rid of in this manner would be very large, it might, in doubtful cases, be just enough to turn the scale in favor of the patient. In this connection, however, it should be remembered that such radical treatment is not without danger, predisposing as it must to infection, and leaving as an aftermath scars, cicatricial contractures, etc. For these reasons it would hardly be justified in cases in which the size and species of the snake or the location and character of the bite, point towards a favorable prognosis. As stated previously I feel that the rendering of material aid to patients who are really in danger from snake poisoning is a matter requiring the nicest judgment and discrimination which may best be exercised with a thorough understanding of the different points already considered under mortality and prognosis.

In regard to the chemical destruction or neutralization of the venom, it must be emphasized to begin with, that this is only possible in the tissues around the wound, and that it is impossible in any way to affect the venom itself once it passes into the general circulation, save by the use of specific antisera. Obvious as this is from the very nature of the poison, one still reads reports of cases in which various drugs are given hypodermically or by mouth, not as stimulants, but with the idea of acting directly on the venom. Among the drugs which have

the undoubted power to destroy or very materially decrease the toxicity of snake venoms if brought in contact with them in a sufficient degree of concentration, potassium permanganate has attained the most widespread use. The use of this drug has been especially championed by Brunton and Fayer,[62] who recommend that the pure crystals be rubbed into incisions made through the fang punctures. Others use a 1 to 100 solution injected deeply into the tissues around the bite. Most observers believe that the use of potassium permanganate is attended with a diminished mortality. In company with others, however, McFarland[40] has little faith in it, and advocates the hypodermic use of a 10 per cent. fresh watery solution of chlorid of calcium. Solutions of iodin and potassium iodid, of chlorid of gold, and of chromic acid, have all been recommended in this connection. Much that has been said in regard to the abstraction of venom from the tissues will apply with equal force to the use of any of these various chemicals. The question of their efficacy does not hinge on their power favorably to alter the poison, which is unquestioned, but on being able to get them in contact with it in a sufficient degree of concentration. Their use promptly after the bite, preferably through a free dissection of the bitten part, will undoubtedly destroy some of the venom, and by just so much affect the outcome of the case favorably. Their use later, in cases as usually first seen, probably destroys so little of the poison, as to make it a procedure of very doubtful expediency.

In concluding the consideration of the local treatment it is necessary to emphasize the great importance of the application of the principles of aseptic and antiseptic surgery to these cases: The great predisposition to local infection and the important part played by it in causing death, have been already pointed out, and the taking of proper precautions to guard against its occurrence becomes a matter of prime necessity. Once present, infection, or any other local complication, as gangrene, should be treated along general surgical lines. That amputation may occasionally be necessary in these cases, has already been mentioned in considering the complication. A degree of local swelling endangering the vitality of the skin is probably best treated by free incision.

It now remains to be seen how much can be done in the way of aiding the system at large in its effort to overcome the venom absorbed from the local focus. The condition to be treated is essentially a toxemia, and the various symptoms observed are due to the manifold

62. Brunton, Fayer and Rogers: A Method of Preventing Death from Snake-bite, Capable of Common and Easy Practical Application, Proc. Roy. Soc., Lond., 1904, lxxiii, 323; also Indian Med. Gaz., 1904, xxxix, 327.

activities of the various toxic principles contained in the circulating poison. Looking at the matter from a broad general view point the therapeutic indications are perfectly obvious, namely:

1. To destroy the source of the poison.
2. To destroy or neutralize the poison already in the circulation.
3. To aid in and to stimulate its elimination.
4. To support the patient.

All that can be successfully accomplished in the way of eliminating the source of supply of the poison has already been considered; indeed this is the sole object of all the local treatment. The actual destruction or neutralization of the venom already absorbed is, from the very nature of things, impossible save by the use of specific antisera. This ideal treatment will be given the separate consideration which its importance renders necessary. In regard to the general or non-specific treatment, then, there remains to be considered only the means at our disposal to meet the third and fourth indications enumerated above.

So little is known concerning the fate of venom in the body that it is rather difficult to take up intelligently the subject of its elimination. It has been asserted that some of the venom is excreted by the gastric mucosa, and to prevent reabsorption its removal by gastric lavage has been recommended. The experiments made to determine the toxicity of venom administered by mouth indicate so clearly its almost complete harmlessness when taken in this way, that stomach washing would seem to be worse than useless. Whatever poison is excreted in this manner is probably promptly destroyed by the digestive secretions. The kidneys, skin, and bowels should, of course, be kept properly functionating, preferably by a free gratification of the thirst often present, or by the use of physiologic salt solution, which will be considered later.

The general support of the patient during the period of absolute collapse so characteristic of venom intoxication, is of the utmost importance. Here common sense, and a knowledge of the ordinary means used in combating such a condition when due to more frequent causes, will be of greatest value. The patient should of course be kept quiet and warm, in the reclining posture with the head low, and artificial heat applied to the extremities.

Of the long list of stimulants urged on the profession at various times as being of service in this condition, but three need be mentioned specifically. These are alcohol, strychnin, and ammonia. Alcohol, as ordinarily used, is much worse than useless. Reflection on the subject fails to show any ground on which a claim that it is in any sense antidotal to or destructive of snake venom, may be based. When used in

the enormous doses so often referred to in the literature there can be no doubt that alcohol poisoning is added to venom poisoning, and the system taxed just so much the more. More patients have recovered in spite of its use, than because of it. It is well worthy of note of the 78 fatalities in the series of collected cases, four, or over 5 per cent., were attributed by the attending physician to the excessive use of alcohol. In a case reported to me by Dr. Fitzsimon, a boy of three years had been given, before being seen by a physician, over a pint of whisky. The patient died in convulsions. Strychnin has been warmly advocated by Mueller of Australia, and condemned with equal warmth by many observers. It has been used considerably in India and Australia in cases of colubrine poisoning, in which the decided primary depression of the respiratory center would seem to indicate its use, if at all. Nevertheless 113 patients treated with strychnin gave a mortality of 13.2 per cent. and 313 without it a mortality of 4.1 per cent. (Huxtable). Animal experimentation has also shown only bad effects from its use (Noguchi). On theoretical grounds, it would seem to be much less strongly indicated in crotaline than in colubrine poisoning, and its value, and that of ammonia also, in treating the bites of American snakes, may be considered to be decidedly dubious.

In regard to the whole subject of stimulation, it must be remembered that the condition of both circulation and respiration in these cases is, in the main, due to the direct activity of the venom on the vasomotor and to a less degree on the respiratory centers, and that this action, from the beginning, is probably much more than a mere functional depression. What we have to deal with in all probability are definite changes in the make up of the nerve cells; changes of a cytolytic nature which can be demonstrated microscopically when death has not been too rapid. Under these circumstances the writer can see little hope of much benefit to be derived from the exhibitions of stimulants.

The conclusions of Rogers[9] as a result of his study of several viperine venoms, including that of the rattlesnake, have already been mentioned in considering the various toxic actions of venom. Briefly these are that, clinically, the most important toxic activity of rattlesnake venom is its profound lowering of blood pressure, to a point where the weakened respiratory center fails to act and death results, and that this result is due to the direct action of the venom on the vasomotor center, determining a dilatation and engorgement of the portal system. The investigations of Mitchell and Reichert[5] demonstrated the occurrence of this fall of blood pressure in experimental poisoning with rattlesnake, copperhead, and water moccasin venoms.

Nowhere are there experimental findings of more practical importance than in this country, and the simple therapeutic procedures recommended by Rogers as a result of them, are worthy of a thorough trial by those who have cases of crotaline poisoning to treat. For it is obvious that if the circulation can be maintained by increasing blood pressure, the danger of secondary respiratory failure is greatly decreased and the patient may be tided over the crucial point of the disease. The mechanical means advocated in attaining this end, tight bandaging of the limbs and abdominal compression by means of a binder, have not been tried clinically. Menger,[63] however, argued for the use of adrenalin, on theoretical grounds, in 1903; in 1905 he[64] reported a case of water moccasin bite successfully treated by the combined use of potassium permanganate and adrenalin. Hooker[65] has reported a case of rattlesnake bite in a boy of ten years treated with adrenalin and salt solution. The patient made a rapid recovery. Lewis[66] has reported a fatal case of rattlesnake bite in a boy of fourteen years in which adrenalin was used in conjunction with strychnin and ammonia. The well-known action of adrenalin on blood pressure, and the way in which it is brought about, by a direct action on the muscular fibers of the vessel walls, would certainly seem to point to its being of value in these cases, and its administration would at least appear to rest on a much sounder basis than does indiscriminate stimulation with alcohol and strychnin, now so much in vogue.

Another drug, which on theoretical grounds appears to be worthy of an extended trial, is physiologic salt solution. Its use has been advocated by Hooker,[65] who points out that its action is threefold, stimulating the heart, stimulating elimination by the kidneys, and diluting the poison. In severe cases the administration of salt solution by intravenous injection would seem to be strongly indicated and in cases of less severity its use by enteroclysis or hypodermoclysis could, to say the least, do no harm. The solution may be impregnated with oxygen.

Artificial respiration has been found experimentally to be by no means the life-saving process in cases of viperine poisoning which it undoubtedly is in colubrine poisoning (Rogers). In fatal cases of rattlesnake poisoning the circulation usually comes to a standstill

63. Menger, R.: The Rational Treatment of Snake-bite and Others with Adrenalin Chlorid, Texas Med. Jour., Austin, 1902-03, xviii, 445.

64. Menger, R.: Moccasin-Bite Treated with Adrenalin Chlorid Solution, Texas Med. Jour., Austin, 1904-05, xx, 263.

65. Hooker, J. D.: A Case of Snake-Bite Treated with Adrenalin Chlorid Solution, Texas Med. Jour., Austin, 1903-04, xix, 87.

66. See Case 13, Table 2.

before the cessation of respiration.[67] The greater tendency of the ancistrodon venoms, both copperhead and water moccasin, to attack primarily the respiratory center has been pointed out, and in severe poisonings by the bite of either of these snakes, or of a coral snake, artificial respiration might well prove to be life saving. Such was certainly the case in the copperhead poisoning reported by Crum,[22] to which reference has been made, and this means of treatment should certainly be faithfully employed so long as the heart continues to beat.

In concluding the consideration of the treatment of snake poisoning in the United States, there remains to be discussed the use of antisera. It is not my intention to enter at all deeply into this subject, and readers particularly interested are referred to the exhaustive consideration of it by Martin and Lamb.[7] These authors have pointed out that "antivenomous serums are highly, but not strictly specific," which means that in order to attain anything like satisfactory therapeutic results, the antivenomous serum used in combating a case of snake poisoning must have been prepared by using the venom of the particular species of snake inflicting the bite. From this it follows that an antivenomous serum to be of any practical value in the United States must have been obtained from animals immunized against crotaline venoms. No such serum is obtainable commercially. Noguchi has prepared sera with marked antitoxic properties against rattlesnake and moccasin venoms, but only on an experimental scale. It is obvious, then, that such a thing as the serum treatment of snake poisoning, so far as this country is concerned, simply does not exist.

Nor is it likely that it ever will. The difficulties in obtaining a sufficiently large supply of venom to render possible the production on a commercial scale, of an antivenene, could only be obviated by breeding large numbers of snakes in captivity, and even with a large and continuous supply of venoms there would still remain to be overcome the difficulties pointed out by McFarland,[40] the severe local reaction and likelihood of infection in the animals used. Having succeeded in overcoming all these difficulties the value of a serum so prepared even if it could be made polyvalent, i.e., protective against all of the three pit viper venoms, would be dubious, unless it could be made more potent than Calmette's serum. As pointed out by Martin and Lamb[7] this serum in doses of 1 c.c. protects a guinea-pig against only 10 minimum lethal doses of the cobra venom while the same amount of diphtheria antitoxin protects against 100,000 minimum lethal doses of the toxin, and an equal amount of tetanus antitoxin against 200,000 minimum

67. See Case 10, Table 2.

lethal doses of the tetanus toxin. It is doubtful, finally, if the morbidity and mortality from snake bite in the United States will ever demand the preparation of an effective antivenomous serum. Such reasoning, however, certainly does not apply to India, with an annual number of deaths from this cause amounting to about 20,000.

GENERAL SUMMARY AND CONCLUSION.

I wish to lay special stress and emphasis on the following points which I hope have been brought out in this article:

1. Technically speaking it is correct to say that there are over twenty species of poisonous snakes found in the United States, but it is decidedly less misleading, at least from the view-point of the physician and therefore in medical literature, to place the number at four, the coral snake, the rattlesnakes, the copperhead, and the southern water moccasin, qualifying this with the statement that two species of coral snakes and several of rattlesnakes are recognized by herpetologists.

2. These snakes are all found together only in the group of states roughly indicated as extending from mid Texas to the Carolinas, inclusive, the remainder of the country harboring at most not more than two of the four mentioned.

3. The presence of a pit between the eye and nostril, on the side of the face, or of undivided ventral scales on the tail immediately stamp a snake as dangerous, and the absence of these points indicates the harmless character of any snake in the United States, with the single exception of the gaudily colored coral snakes, confined entirely to the southern states.

4. While it is impossible to state the morbidity from snake bite in the United States, it is undoubtedly excessively small, and over 99 per cent. of it is due to the crotaline snakes, or pit vipers.

5. The most important complications of snake bite are sepsis and acute alcoholism, probably respectively responsible for about 10 per cent. and 5 per cent. of the fatalities.

6. The mortality of all cases is 10 per cent., that from the different species being as follows: Coral snakes, probably from 25 to 50 per cent.; water moccasins, 17 per cent.; large species of rattlesnakes, 11 or 12 per cent.; copperhead and ground rattlers, *nil* in uncomplicated cases in adults up to about 5 per cent. when all cases are included.

7. Bites on the head and trunk are much more dangerous than those on the extremities, and those on the upper extremity at least twice as dangerous as those on the lower.

8. The mortality in children under ten years of age is at least double that in adults.

9. The local treatment, having for its object the limiting of venom absorption, is of the greatest importance; in order to be effective it must be both prompt and radical; in all surgical procedures around the wound, special precautions must be taken against infection.

10. The ideal constitutional treatment by means of antisera is now absolutely impracticable and, therefore, little can be done other than keeping the patient quiet and warm; the administration of adrenalin and salt solution; the use of such mechanical means as bandaging, abdominal compression, and posture to keep up the blood pressure and circulation in the vital centers; and the institution of artificial respiration when indicated.

In conclusion I wish to express my keen appreciation of the kindness of those physicians and others too numerous to mention who have aided me in my endeavor to collect a sufficiently large number of cases to make the statistics based thereon of some value. It is a very keen pleasure to me to make the following specific acknowledgments: To Dr. George Tully Vaughan and Dr. George M. Kober for most valuable advice and encouragement. To Dr. I. W. Blackburn for his great kindness in superintending the making of, and for retouching, the negatives of Figures 5 and 6; the great clearness and accuracy of these figures is due entirely to Dr. Blackburn, and to Mr. Keefer, the photographer at the Government Hospital for the Insane, Washington, D. C. To Dr. William Hough for aid in making the dissections shown in Figures 5 and 6. And finally to the authorities of the U. S. National Museum, for the negative used in Figure 4, for the permission to make use of Figures 1 and 2, and for the specimen of *Crotalus adamanteus* used in making the dissections mentioned.

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